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Discussion

THOMAS DAVID MOORE

THOMAS DAVID MOORE

1894–1958

Thomas David Moore was born in 1894 in Hopkinsville, Kentucky. He earned the degree of Doctor of Medicine at Vanderbilt University School of Medicine at the age of twenty-two. He was considered a student of extraordinary intelligence and unusual technical skill. Shortly after his graduation he received one of the coveted internships at the Willard Parker Hospital in the summer of 1916. His ambition to become a participant in World War I was soon to be realized when he joined the Medical Corps as a first lieutenant. After discharge from the Army, he obtained an internship at the Madison General Hospital in Madison, Wisconsin for 1919–1920. His desire to become a urologist was firmly established and was thoroughly nurtured by an appointment as a fellow for four years in urology at the Mayo Clinic.

In 1924 Dr. Thomas D. Moore was licensed to practice medicine in Tennessee. He opened his office in Memphis and in addition served faithfully in the out-patient clinics of the Baptist Memorial and John Gaston Hospitals. His thoroughness of purpose, his keen sense of proportion, his superior technical ability, his knowledge of human values, his winning smile, his fund of anecdotes—all his personal attributes—were attributes which attracted patients to him from close and distant places. His unselfish approach to the patient-doctor relationship led him on the road to success.

Dr. Moore's keen vision and intuitive thinking resulted in his writing between fifty and sixty papers covering various diseases in the young and aged patients. Among his chief interests were visualization of the upper urinary tracts with various media, serial x-rays of the kidney, pelvis and ureters, carcinoma of the bladder treated with radium, transurethral and retropubic prostatectomy, calculus disease of the urinary tract, conservation of renal tissue and reconstruction of the bladder neck. His writings would indicate that he spent much time in meditation upon the physiology of the bladder and kidney, pathological lesions both benign and malignant, and by what new methods could a reconstruction be applied to give his patient a comfortable and pleasant future.

Dr. Moore's interest in organized medicine and knowledge of medical values gained for him membership in the American College of Surgeons and all the urological societies. He was among the founders of the Board of Urology. He was an active member in the Southeastern Urological Section, the American Urological Association, the American Association of Genito-Urinary Surgeons, the Clinical Society of Genito-Urinary Surgeons, and the Société de Urologie Internationale. He was generous with his time and served as secretary to the American Urological Association from 1942 to 1949 and became its president in 1950. During these busy years he was professor of urology at the University of Tennessee and shared his knowledge with and transferred to his many students the urological arts.

Those of us who were fortunate to have had close association with Tom Moore realize that his life was complete and filled with devotion and loyalty to mankind. He enjoyed life, he loved people and he made friends. We extend to his children and to his wife, Dorothye, our tenderest sympathies and share with them the loss of a devoted father and husband. May the following lines represent our mutual feelings:

"Ne'er did a sun rise in heaven so high,
With success, loyalty and devotion hard by;
And now his sun has set in the West,
His memory, we cherish with the Best."

CLYDE L. DEMING

SAMUEL ALEXANDER VEST, JR.

SAMUEL ALEXANDER VEST, JR.

1905–1958

The sudden and premature death of Dr. Samuel Alexander Vest, Jr. on April 6, 1958 was a shock to his university community and to his innumerable friends and former patients throughout the whole country. Many will regard his loss as a very personal one.

Dr. Vest was born at Haw River, North Carolina on January 21, 1905, the son of the late Captain Samuel Alexander and Gertrude Roberts Vest. After preliminary education in local schools he matriculated at Duke University from which he received his bachelor's degree in 1926. He then entered the Johns Hopkins University School of Medicine and took his medical degree in 1930.

After graduation he served an internship at the Brady Urological Institute under the late Dr. Hugh H. Young. Upon his selection for the residency there he spent two preliminary years in general surgery and one in general pathology.

He then became an assistant resident at the Brady Institute, and the following year advanced to the residency in urology at the Ancker Hospital, in St. Paul. Returning to Baltimore in 1936 he assumed the residency in urology at the Brady Institute, and served with such distinction that Dr. Young persuaded him to remain in a full-time capacity for one more year. It was during this period that his talent for investigation was generally recognized, and in 1938 he was appointed head of the department of urology at the University of Virginia.

His 19 years in Charlottesville disclose a record of uninterrupted achievement. He rose to a position of eminence on the faculty, earned the admiration and respect of students, interns and colleagues, and won the unswerving loyalty of 19 devoted residents whom he trained. An authority on many aspects of urology, he contributed 65 articles to the medical literature and devised the Vest telescope for improved urethroscopic vision.

Dr. Vest belonged to numerous medical societies and served on important committees of national medical organizations. He was a member of this Association, the American Urological Association, the Clinical Society of Genito-Urinary Surgeons, and was a Fellow of the American College of Surgeons.

His enthusiasm, humor and jolly nature, together with his humility, his appreciation of and kindness to all manner of men, were irresistible, and earned for him universal popularity.

The total impact of his tragic death, on the morning of Easter Sunday, 1958, has not yet been fully felt. He is survived by his wife, the former Miss Sarah Elise Thompson of Graham, N. C., two married daughters, two sons and three grandchildren. The urological profession has lost a teacher, a sympathetic counselor and a friend.

HUGH J. JEWETT

LOUIS E. SCHMIDT

LOUIS E. SCHMIDT

1869–1957

Louis E. Schmidt was born in Chicago, January 8, 1869. He died in Wausau, Wisconsin, July 12, 1957, at the age of 88. He had bought a home in Wausau, Wisconsin, after his second marriage because his only son resided there and many of his second wife's relatives resided there also. His death was due to a number of illnesses from which he suffered during the last few years. His larynx had been removed for carcinoma some ten years ago. He had a gastroenterostomy for an obstructive duodenal ulcer five years ago. He had a two-stage prostatectomy two years ago.

This dynamic and forceful character descended from Dr. Ernst Schmidt, who had come to this country along with many other German liberals during the time of Carl Schurz. He had been a professor of surgery in Wurzburg and was banished from Germany for his liberal views. He spent a year in Italy and six months in England, after which he migrated to St. Louis, Missouri. He helped organize the medical school in what is now known as Washington University. He moved to Chicago one year later. Ernst Schmidt served as a volunteer surgeon in the Civil War with a Missouri regiment of Germans under General Lyon. He returned from the Civil War to practice medicine in Chicago for many years.

Louis was the youngest of four sons. The oldest son was Otto, who practiced medicine in Chicago for many years. Frederick was a pharmacist. Richard, who is the only surviving brother, now 92 years old, is one of Chicago's well known architects.

Doctor Schmidt received his early education in the Chicago public schools. He attended the College of Pharmacy of Chicago and obtained his Pharmacy degree in 1889. He received a Bachelor of Science degree from the University of Michigan in 1892, a Master of Science degree from Northwestern University in 1894 and a Doctor of Medicine degree from the same school in 1895. After his internship in Alexian Brothers Hospital of Chicago, he went to Europe for 30 months of post-graduate work. He studied pathology and urology in Vienna and Berlin. He attended clinics in Paris, Breslau and London. When he returned to Chicago, he became one of the first urologists to practice this specialty west of the Alleghanies.

Doctor Schmidt married Marie Mansfield in 1905. She died in 1918. They had a daughter, Hildegard, who died of multiple sclerosis at the age of 35 and a son, Mansfield, who died of coronary thrombosis at the age of 38. Hildegard's son, Mansfield Templeton, lives in Weston, Connecticut. Mansfield's daughter, Hildegard, lives in Fort Myer, Florida. Doctor Schmidt remarried in 1942. The second wife's name was Mrs. Lilliam D. Stevens. She died in 1956.

Doctor Schmidt was the first professor of genito-urinary surgery of Northwestern University Medical School. He was appointed in 1899. He served as head of the Department of Urology until 1946, when he was made a professor emeritus. Northwestern University conferred a Doctor of Science degree upon him in 1942. At the time of his retirement from active practice in Chicago, he was a senior attending urologist of St. Luke's Hospital and a consulting urologist for Passavant and Grant Hospitals. During his 50 years of active practice in Chicago, he had been connected as a staff member or consultant, with Alexian Brothers, Michael Reese, Wesley and St. Mary's Hospitals. He was a member of the advisory board and a consultant at Great Lakes Naval Training Station during World War I.

Doctor Schmidt wrote widely on urological subjects. In 1910, he wrote on "Series of Unusual Cases with Pathological Conditions Outside of the Bladder causing Marked Vesical Symptoms;" in 1911 "The Complement-Fixation Test in Gonorrhoea," "The Diagnostic Value of the Shadowgraph Catheter," and "The Phenolsulfonephthalein Test in Surgery of the Genito-Urinary Tract." In 1911–12, when Doctor Schmidt was president of the American Urological Association, his presidential address was entitled "Why Urology should be considered a Specialty." He wrote about "Surgery of the Urinary Bladder" in 1915, and "Focal Infection of the Genito-Urinary Tract" in 1917. He was the leader in the celebrated Chicago campaign against venereal disease. This campaign spearheaded the national drive against syphilis.

Those men who served a preceptorship under Dr. Louis Schmidt will always remember him as a good teacher, a severe task maker and a tireless worker. Many of his assistants became leaders in American urology.

His knowledge of people in and around Chicago was tremendous. Every Christmas found him distributing monetary presents to all of his daily contacts. Every New Year's Eve found him entertaining lavishly in his home, people from all walks of life.

He was a Fellow of the Institute of Medicine of Chicago and its vice-president in 1927. He was also a member of the American Medical Association, and the American College of Surgeons. As stated above, he was a member of the American Urological Association and its president in 1911–12. Doctor Schmidt was elected to membership in the Association of Genito-Urinary Surgeons in 1903. He was our vice-president in 1916. He was our president in 1919. We elected him an honorary member in 1948. He was elected a member of the Clinical Society of Genito-Urinary Surgeons in 1922. He was a Fellow of the American Public Health Association and the American Hygeine Association. His medical fraternity was Nu Sigma Nu. He was also a member of the Chicago Athletic Association, University Club of Chicago, Chicago Yacht Club and the South Shore Country Club.

I am very grateful to Dr. T. P. Grauer, who was associated with Doctor Schmidt, and to Mrs. W. F. Petersen, a niece of Doctor Schmidt, for their help in preparing this brief summary of the life of a man who did so much for the development and recognition of urology as a specialty.

WILLIAM J. BAKER

SUBTOTAL CYSTECTOMY FOR INFILTRATIVE CARCINOMA OF THE TRIGONE

BEN D. MASSEY

Definitive treatment of infiltrating carcinoma of the bladder trigone is usually considered to require cystectomy. The ease with which one recommends such a procedure depends upon his enthusiasm for the method of urinary diversion currently in vogue. There is much current literature and general discussion about the treatment of carcinoma of the bladder. There is probably no phase of urology in which there is more confusion, where there has been more dogmatism in trying to lay down principles of treatment, or where we have changed the dogma faster or more frequently.

At a time when there is so much enthusiasm for cystectomy and various forms of urinary diversion, I wish to present this case as a gentle reminder that we must first consider every possible method of attack that will maintain normal vesical function. This is expecially true if the bladder is deeply involved and treatment has a high risk of being palliative, rather than curative; and it may be applied to single infiltrating tumors of moderate size, in an otherwise normal bladder, irrespective of location.

CASE REPORT

A 64-year-old white man was admitted to St. Luke Hospital, Pasadena, California, on September 1, 1954, for hemorrhoidectomy. A consultation was requested because of the persistent finding of 15–30 red blood cells in the urine. Cystoscopy was refused and hemorrhoidectomy was done. Moderate dysuria and urgency developed and a cystoscopic examination was finally made on November 29, 1954. This revealed a coalescing, infiltrating carcinoma of the trigone extending into the bladder neck and the right lateral lobe of the prostate, and covering and obstructing the right ureteral orifice. The left ureteral orifice was partially obscured by bullous edema but was not obstructed and the left kidney and ureter appeared normal (fig. 1, *A*). A specimen taken for biopsy was reported "Infiltrating transitional cell carcinoma of the bladder grade 3."

A physical examination revealed no other obvious serious physical defects. The x-ray film of the chest was negative. No anemia was present and the cardiovascular system was considered adequate for the surgical risk.

Surgery was carried out on December 9, 1954, under spinal anesthesia, through a suprapubic midline incision. The bladder was opened well above the bladder neck. The tumor was electrosurgically cut flush with the bladder mucosa and electrocoagulated. The lateral attachments of the bladder were cut and ligated at the pelvic wall with complete disregard for the blood supply of the dome. The bladder was then divided by tangential incisions meeting in the center of the posterior wall. The remaining cap of bladder with its peritoneal attachment undisturbed was retracted (fig. 1, *B*). The ureters were severed 3 cm. above the bladder. The seminal vesicles, trigone, and five-sixths of the prostate were removed. The ureters were then mobilized, intubated with 7F catheters, and transplanted into the remaining portion of the bladder. The right ureter was 12 mm. in diameter. It was transplanted by the everted cuff method. The normal left ureter was transplanted by a simple pull through. Both ureteral catheters and a 24F dePezzer were brought out through a stab wound in the remaining portion of the bladder.

The posterior and anterior edges of the bladder were then approximated like a coin purse by interrupted sutures of size 1 chromic catgut over an inlying 24F Foley urethral catheter. The reconstructed bladder was attached to the prostatic urethral stump by two interrupted sutures of size 00 chromic catgut placed alongside the Foley catheter. The new bladder then was easily held down by two laterally placed Vest sutures of size 2 chromic catgut brought out through the perineum (fig. 2). The urethral catheter was left inlying without tension with the bag inflated to 60 cc with water. The suprapubic wound was closed about the ureteral and dePezzer catheters.

Abstract of pathology report: The specimen consisted of an almost totally resected prostate in continuity with the lower portion of the bladder, seminal vesicles, 3.5 cm. of vas deferens,

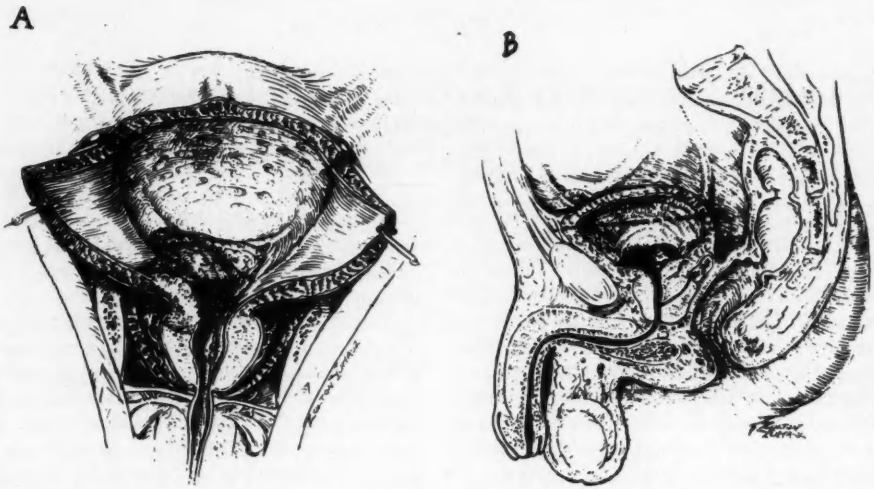

FIG. 1. *A*, open bladder shows position of lesion on bladder trigone and invasion of prostate. *B*, lateral view; line of incision through bladder shown by dotted line. Reconstructed bladder formed by tissue above.

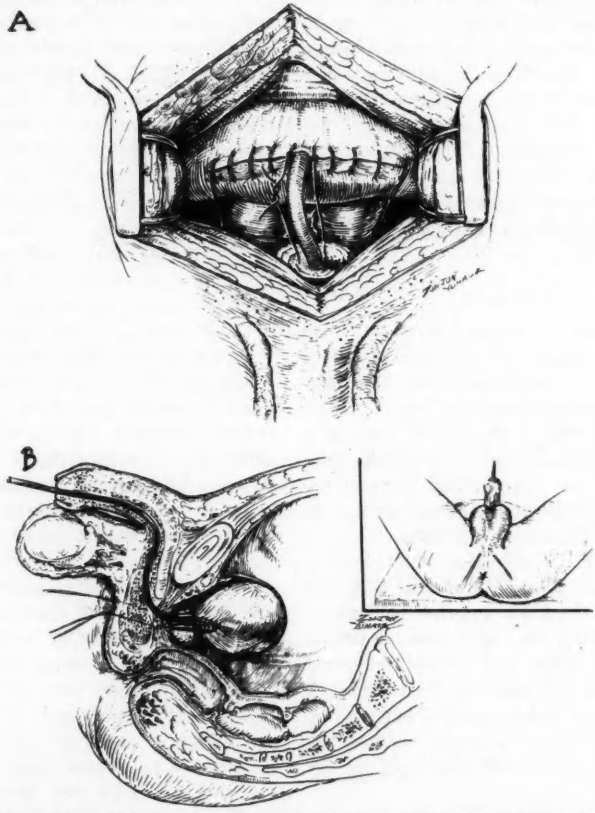

FIG. 2. *A*, method of closure of bladder cap. *B*, lateral view, urethral catheter and traction sutures in place. Ureteral stump shows position of ureteroneocystostomy. Note: Suprapubic tube and ureteral catheters (not shown) were brought out through suprapubic incision.

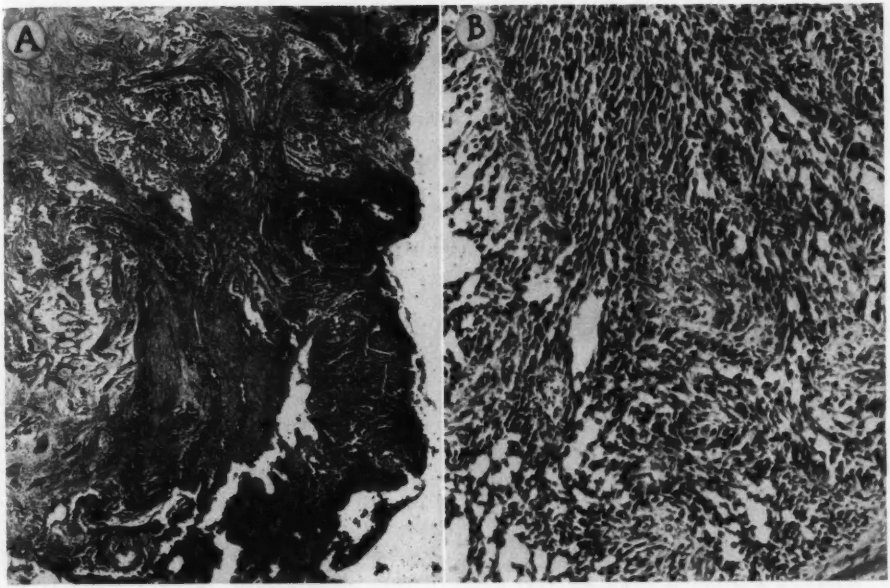

FIG. 3. *A*, low power photomicrograph shows muscular invasion by tumor. Intact bladder mucosa along right margin. *B*, high power photomicrograph shows cellular detail.

FIG. 4. Excretory urogram, 3½ years after ureteroneocystostomy. Ten-minute film shows sharp calyces and dye entering bladder. Right kidney now functioning.

surrounding perivesical fat, and connective tissue. The bladder tissue was distorted by a nodular, dense growth of tumor tissue appearing grossly like a large median lobe. Sections through the frontal plane of the mass showed the tumor extending far laterally in the prostate particularly to the right. Microscopically, the section of primary tumor showed extensive infiltration of bladder muscle by cords and nests of large, bizarre cells with hyperchromatic nuclei and many mitoses (fig. 3). Diagnosis: Infiltrating transitional cell carcinoma, bladder neck (grade 3 Broders); metaplasia, prostatic urethral mucosa; prostatic hyperplasia; prostatitis, chronic, at base of tumor.

Postoperative course: The postoperative course was remarkably smooth. There was little or no fever. A regular diet was promptly resumed. The right ureteral catheter was removed from the dilated right ureter on the seventh postoperative day. The left ureteral catheter and the suprapubic tube were removed on the eleventh postoperative day and the urethral catheter on the fifteenth postoperative day. Pain in the left chest, probably embolic in origin, occurred on

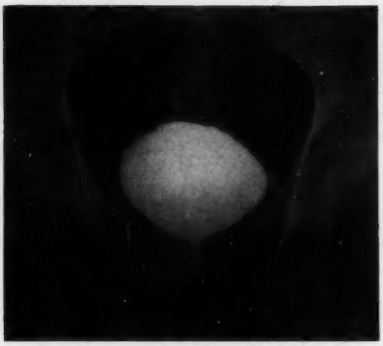

FIG. 5. Cystogram, immediately after straining to void, no reflux; 500 cc capacity.

the thirteenth postoperative day. The patient left the hospital, voiding normally, on the nineteenth postoperative day.

It is now almost three and one-half years since surgery. There is no evidence of recurrence of cancer. Gradual improvement has taken place in the function of the damaged right kidney, as demonstrated by the urograms (fig. 4). There is no ureteral reflux. The bladder capacity is 500 cc without overdistention (fig. 5). There is only occasional nocturia and the urine remains microscopically negative. Urinary control is perfect and sexual potency returned within six months after surgery. At the last cystoscopic examination on March 15, 1958 the bladder appeared normal. The two ureteral orifices are on the posterior wall. They are small and flat. They have never been catheterized.

DISCUSSION

The human bladder has tremendous regenerative and recuperative powers. In the past 60 years there have been isolated reports of remarkable instances of the recovery of bladder function in humans after severe injury and subtotal or total destruction. Considerable laboratory work on animals proves that true regeneration of the bladder does occur. With these published reports as a basis, further work on animals and humans might develop techniques for establishing substitute or new urinary reservoirs far superior to methods of urinary diversion now in vogue.

Of importance in the case reported here is the blood supply of the remaining bladder cap. How much was it receiving and how much was it acting as a free graft? Its only possible source of supply was from its undisturbed peritoneal attachment. In spite of the lack of obvious supply it showed remarkable viability, producing good ureteral anastomoses and regenerating to a bladder of normal size. This leads one to wonder whether it is necessary to reconstruct a bladder after extensive resection? If reconstruction is impossible, are the chances of satisfactory regeneration enhanced if patches of normal bladder are left in place, irrespective of location? The answer to the first question seems to be "no," and to the second question "yes." In point, is a case report presented before this society in 1939 by Dr. Ira Sisk. An attempted cystectomy for carcinoma was abandoned because of technical difficulties and hemorrhage. A 3 cm. square piece of bladder remained in place on the right posterior wall. The severed ureters were left dangling in the pelvis. Within eight weeks the patient was voiding through the urethra and three months later a cystogram indicated maximum bladder regeneration in the region of the retained piece of bladder.

The development of satisfactory ureteroneocystostomy is the key to success in the regeneration of the bladder of either the reconstructed or non-reconstructed type. I believe a satisfactory bladder could be obtained by doing conventional types of ureteral anastomosis to attached patches of normal bladder left after subtotal cystectomy without complete reconstruction of the bladder, allowing regeneration to emanate from these selfsame areas.

Perhaps this case report will focus interest on and promote investigation into this intriguing problem. If it encourages urologists to be more definitive in the surgical excision of single invasive tumors located in critical areas, or if it saves one other patient from unnecessary cystectomy, the report will have been worth while.

CONCLUSION

This is a single case report of infiltrating carcinoma of the bladder trigone, invading the prostate and obstructing the right ureter, successfully removed by wide excision with preservation of renal, vesical, and sexual function.

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TOTAL PROSTATECTOMY WITH PRELIMINARY LIGATION OF THE VASCULAR PEDICLES

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Early carcinoma is a term in general use to describe a localized malignant growth, one which is so limited in extent that its removal will effect complete elimination of the disease. In the absence of positive subjective and objective symptoms we have no method for determining the limits of a suspected early growth prior to its surgical removal. Our only means for determining whether a growth has been removed early enough is the length of survival of a patient without evidence of recurrence following removal.

Local or distant recurrence of a neoplasm following extirpation of a primary growth suggests either incomplete removal of the tumor or the presence of unrecognized metastasis prior to the initial surgery. There are two other possibilities which have received little or no recognition in radical prostatic surgery, namely, local contamination and the dissemination of cancer cells incident to the manipulation of malignant tissues at the time of the surgical procedure. How frequently this occurs in prostatic surgery is impossible to determine at the present time for a statistical review.

Urologists have recognized the possibility of dissemination in renal carcinoma for a long time and have advocated preliminary ligation of the renal vessels prior to manipulation of the tumor. To the present time this principle has not been applied to prostatic surgery.

Without too vigorous massage, secretion can be expressed from a malignant prostate gland, in approximately 85 per cent of which malignant cells can be demonstrated by the Papanicolaou method. More vigorous manipulation with retractors and the finger required to remove a malignant prostate gland surely must result in expression of prostatic fluid that contains viable malignant cells which can be the cause of local recurrence.

Recently, Roberts and associates[1] demonstrated the actual increase of tumor cells in the venous blood during the manipulation of malignant lesions. Included in these studies were patients with renal and vesical neoplasms. Prostatic carcinoma was not included in this study. However, it is reasonable to believe that its action would be similar to bladder carcinoma as well as the other organs studied. The possibility is sufficiently real to require re-evaluation of our present methods for radical prostatectomy.

At a meeting of the New York Urological Society in 1943, Dr. James Ewing, a pathologist, remarked after seeing a motion picture of a radical prostatectomy, "If an attempt had been made to devise an operation to spread cancer, one could not have done better than this." The traction and manipulation required, especially with an enlarged gland, prior to ligation of the vascular channels amount to an extremely vigorous massage.

The retropubic approach is being widely advocated and used at present, possibly because of a more general familiarity with the suprapubic operation on the prostate gland and a reluctance to learn the perineal operation. The technique described for retropubic total prostatectomy does not consider the possibility of manipulative dissemination. The gland is frequently grasped with forceps and considerably manipulated before the vascular and lymph channels are sealed to prevent the possible extrusion of malignant cells beyond the anatomic capsule.

The suprapubic route does permit a more ideal approach to the problem by closing the vascular and lymph channels from the prostate gland preliminary to manipulation for its removal. This can be done very simply by reversing the present technique of removing the gland and seminal vesicles as described in the following procedure.

OPERATION

The bladder is approached through a midline or transverse suprapubic incision as one desires. The anterior wall of the bladder is exposed down to the prostate gland. Pressure on the anterior

[1] Roberts, S., Watne, A., McGrath, R., McGrew, E. and Cole, W. H.: Technique and results of isolation of cancer cells from the circulating blood. A.M.A. Arch. Surg., **76:** 334–345, 1958.

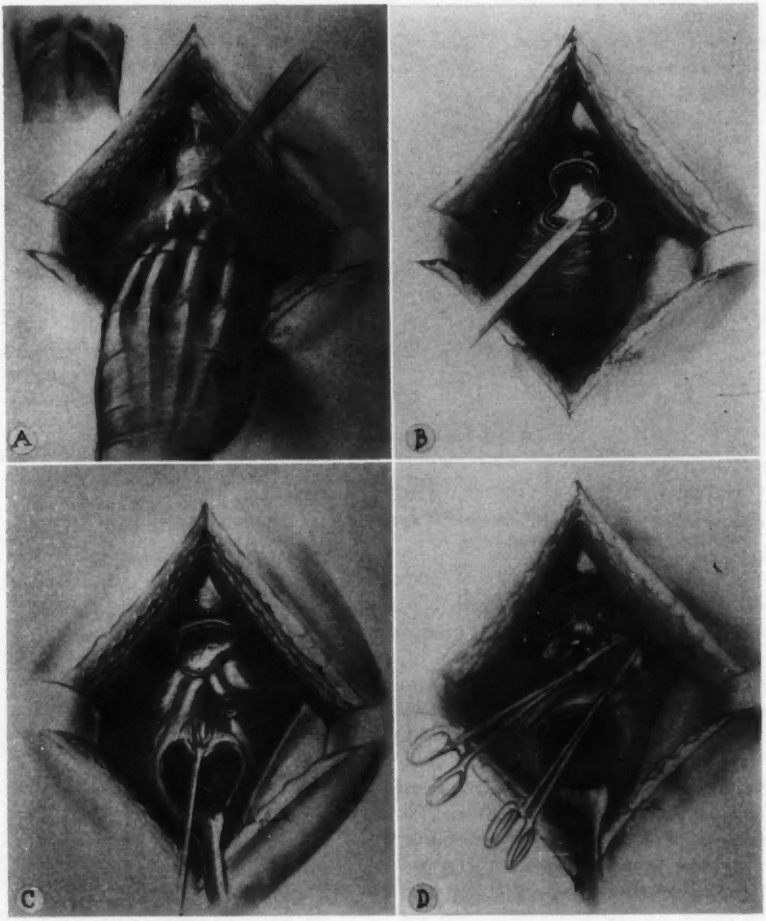

FIG. 1. *A*, anterior bladder is incised transversely above its junction with prostate. *B*, bladder is resected from prostate to edges of trigone. Trigone is cut transversely in downward and posterior direction to avoid ureters. Incision is extended through vesical wall to completely remove bladder from prostate. *C*, posterior wall of bladder is turned upward and forward to expose seminal vesicles. Vesicles and vasa are dissected with their surrounding fascia from rectum. *D*, vascular pedicles are isolated by blunt dissection lateral to prostate and posteriorly by dissection lateral to rectum. These are clamped, cut and tied.

wall with the fingers on a sponge will permit accurate identification of the vesicoprostatic junction and make the wall sufficiently tense to facilitate its incision. The anterior wall of the bladder is incised transversely, preferably with a knife, immediately above its junction with the prostate gland (fig. 1, *A*). The bladder is opened and any residual urine evacuated. This incision is extended laterally and posteriorly around the neck of the bladder, leaving a small cuff of bladder wall attached to the prostate gland. The bladder is cut away from the gland to a point one to two centimeters lateral to the edges of the trigone. The entire bladder base and vesical outlet can now be visualized. A transverse incision is made with a knife across the trigone through the entire bladder wall to unite the lateral incisions (fig. 1, *B*). This incision is made as close as possible to the vesical neck, but sufficient tissue must remain to insure complete removal of

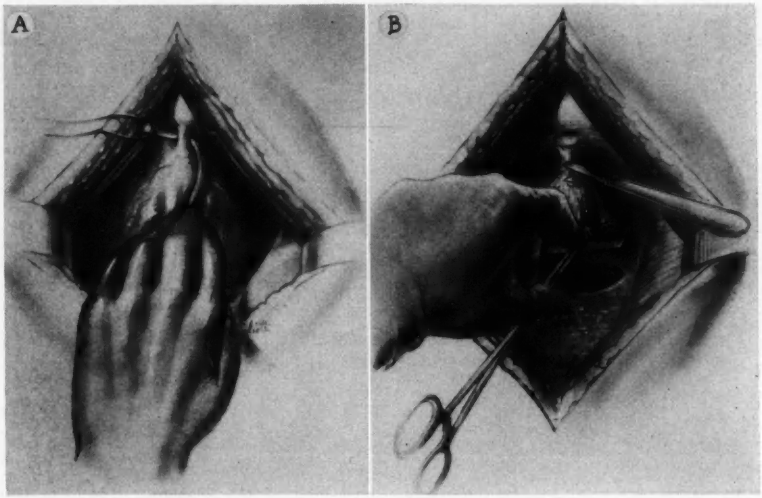

FIG. 2. *A*, anterior veins and puboprostatic ligaments are tied and severed from prostate. With this procedure all venous exits from gland have been closed. *B*, urethra is severed at apex of prostate gland. No glandular tissue should remain.

all malignant tissue. At this point it must be remembered that the detrusor fibers turn forward to converge at the vesical neck. Therefore, this incision must be made in an obliquely downward as well as posterior direction in order to avoid the ureters. The entire bladder wall is transected to a line of cleavage between the outer surface of the posterior vesical wall and the connective tissue surrounding the seminal vesicles and vasa. The posterior vesical wall is bluntly dissected from these tissues and turned upward and forward until the seminal vesicles are completely exposed.

The tips of the seminal vesicles are freed and the attached vessels clamped, cut and tied. The vasa are tied and cut at the same level (fig. 1, *C*). Both structures with their surrounding tissues are dissected from the rectum to the base of the prostate gland.

Blunt dissection with forceps anterior and lateral to the base of the prostate gland and dissection lateral to the rectum on each side will isolate the main vascular pedicles (fig. 1, *D*). These are clamped, cut and tied with No. 2 chromic catgut. The main lymphatic and vascular exits are now blocked and the prostate gland has not been touched.

The anterior vessels and the puboprostatic ligament are now ligated (fig. 2, *A*). The exposure of these structures can be facilitated by grasping the cuff of bladder muscle attached to the prostate

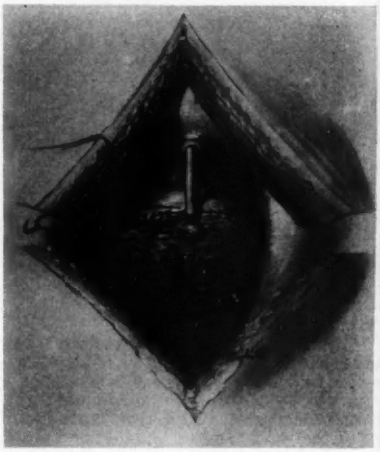

FIG. 3. Bladder opening is closed either transversely or vertically with interrupted catgut sutures around a size 22 Foley catheter. Type of closure is varied depending on ease with which bladder can be approximated to urethra.

gland anteriorly with Allis forceps and exerting gentle downward pressure. A curved clamp may be passed around these structures to carry a ligature as described by Chute.[2] This procedure frequently requires more manipulation than clamp

[2] Chute, R.: Radical retropubic prostatectomy for cancer. J. Urol., **71**: 347–372, 1954.

ing the entire structure with a large Kelly clamp, severing these structures from the prostate gland and ligating the clamped tissues.

The apex of the prostate gland is exposed and the urethra severed transversely distal to the apex of the gland (fig. 2, *B*). No glandular tissue is allowed to remain.

A soft rubber catheter is passed retrograde through the isolated prostatic urethra, picked up at the distal end, looped forward and used as a retractor for the removal of the gland. The apex of the gland is lifted and Denonvilliers' fascia is carefully dissected from the rectum. With this last step the gland should be completely free to be removed if the seminal vesicles have been carefully mobilized and the vascular pedicles accurately ligated.

A size 22 Foley catheter is inserted through the distal urethra and fed into the bladder. The bag is filled with 25 cc water. The bladder is closed either transversely or vertically depending on the ease with which the bladder can be approximated to the urethra (fig. 3). The bladder is closed with interrupted size 1 chromic catgut sutures. Traction is placed on the distal end of the catheter to obtain approximation of the bladder and urethra without pressure. The catheter is fastened to the thigh with the anastomosis under vision so the exact amount of tension is assured.

Penrose drains are inserted, one to each side of the bladder base and brought through the lower angle of the wound. The wound is closed with interrupted figure 8 silk sutures.

The traction on the catheter is gradually released by the catheter slipping under the adhesive tape fastenings to the thigh; so there is little or no traction at the end of three days. The catheter is removed on the tenth postoperative day, and the patient discharged two days later.

This technique has now been used by us on eight patients. The amount of bleeding has been insignificant. Visibility has been exceptional for every stage of the operative procedure. Urinary leakage occurred in two patients, one for three days and the other for five days following removal of the catheter. Six patients had immediate, complete control of urine. One had stress incontinence for four weeks. Another had control when sitting and when recumbent, but was practically incontinent when on his feet. This continued for exactly 90 days when he gained complete control and has remained continent. None of the patients have required the passage of sounds for stricture at the site of anastomosis.

It will require study of many patients over a long period to compare this method with the enviable records which Dr. Hugh J. Jewett and Dr. Elmer Belt have presented. The change in the approach to the problem of prostatic carcinoma as suggested in this paper, if adopted, may help increase the survival rate, for I believe the tenet presented is sound.

SUMMARY

The dissemination of cancer cells into venous channels by the manipulation of malignant tissues has been demonstrated sufficiently to warrant a re-evaluation of our methods for total prostatectomy. The techniques now in use do not consider this probability.

An operation is described which minimizes the possibility of dissemination by ligation of the vascular pedicles before the malignant gland is manipulated.

The operation in no way complicates or lengthens the established procedure.

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DISCUSSION

DR. JOSEPH H. KIEFER (Chicago, Ill.): I wish to say a word on Dr. Massey's paper. I had a case just two months ago very much like his, only in a woman about 70 years old who had an infiltrating tumor involving the left orifice and coming right up to the edge of the urethral opening. In order to resect the tumor I took the urethral opening, the entire trigone up to the right ureteral orifice and a goodly portion of the left half of the bladder.

[Demonstration] The bladder was reconstructed around a Foley catheter. A portion of the remaining right lateral wall was sutured around the catheter and brought down against the remaining urethra and held with Vest sutures through the perineum.

The left ureter was implanted into the most adjacent portion of the upper part of the bladder. This was the first time I had ever resected the entire urethral opening. I was amazed that the postoperative course was no more complicated than other partial resections of the bladder. The suprapubic tube was out in eight days. The Foley catheter below was out in 12 days. She voided almost immediately, with perfect control.

I had always been taught that one could not remove the vesical neck without doing a total cystectomy but this rule does not always hold.

DR. JUSTIN J. CORDONNIER (St. Louis, Mo.): Dr. Massey is to be congratulated on an excellent result. However, I should like to offer one word of criticism. It seems to me that both Dr. Massey and Dr. Kiefer are not doing what I would term good cancer surgery. I don't believe that a partial resection involving part of the prostate and leaving another part is adequate, particularly when one considers the extensive lymphatic network in that area.

Although each reports a good result, I should like to offer a word of caution. Following cystectomy the incidence of recurrence in the male urethra in our series has been three out of 73, after removing the entire prostate and seminal vesicles.

I should think the possibility of local recurrence in the urethra in Dr. Kiefer's case would be very great and if he did 100 of them he would find a considerable number of recurrences. In my experience with bladder cancer we have found that whenever you get too close to the cancer you spread it and it goes like wildfire.

I think both of these procedures are inadequate in spite of their success.

DR. RUBIN FLOCKS (Iowa City, Iowa): I would like to say a few words about Dr. Campbell's paper. A few years ago we made some studies of serum acid phosphatase following prostatic massage, and found that it was elevated. Recently the work that Dr. Campbell mentioned with regard to the finding of tumor cells in the bloodstream associated with radical surgery of any type, in any location, raises the question as to the problem of increasing metastases as a result of manipulation.

I was impressed a few years ago with the results that Dr. Winfield Wentworth Scott, of Rochester, had in his cases of radical prostatectomy with orchiectomy in more advanced patients than are usually considered operable for prostatic carcinoma. Joining those two things together, I wondered whether these cells which were pushed into the bloodstream (if they were pushed into the bloodstream, and you will notice this is a little theoretical) did not fall upon unfavorable soil and did not grow, as, for example, the prostatic tissue that Dr. Green, at Yale, puts into the vitreous humor of the eye does not grow unless the animal is a male, and it is supplemented by the administration of testosterone.

So, in the last year and a half or two we have supplemented radical surgery for early prostatic carcinoma with the preliminary and the continuous administration over a period of a few weeks of large doses of estrogen, the idea being that the cells pushed into vascular channels during operation would not fall on favorable "soil" and would die.

Thank you.

DR. HARRY M. SPENCE (Dallas, Texas): I would like to make just a fringe comment relating to the use of the so-called Vest sutures.

I believe the term "Vest suture" should be restricted to the use of such sutures when placed via the perineum. I believe it was Dr. Chute who proposed the use of similar type sutures placed from above in the retropubic operation. At least he was the first to call it to our attention.

I think such sutures look fine in a diagram, but

are completely unnecessary, and the technique of bringing the bladder neck down by traction on the catheter, as Dr. Campbell suggests, is entirely adequate. The amount of traction one uses is of some moment. Very little traction will suffice. A simple method is to hitch a string to the catheter and pass this string over a pulley at the foot of the bed with about a half pound weight attached to provide gentle but continuous traction.

I have given up the so-called Vest-Chute stitches. I think they are unnecessary.

DR. RICHARD CHUTE (Brookline, Mass.): May I say that those sutures were not original with me. The credit for them belongs to Dr. Lytle Atherton of Louisville. I like them.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I have a question for Dr. Campbell. He very carefully avoids manipulation of the prostate during retropubic operation. I would like to ask him how he makes the diagnosis of carcinoma, to know whether or not to go ahead with his radical operation without manipulation.

DR. WILLIAM J. BAKER (Chicago, Ill.): I would like to direct your attention to a complication which was caused when a bag catheter was used to pull down the remaining bladder to the urethra, after a radical prostatovesiculectomy. Anuria was produced in two patients. One of these cases of anuria persisted for five days before we had presence of mind to deflate the bag. There was immediate free flow of urine. The other case of anuria was permitted to last 48 hours before the bag was deflated. Again, there was a free flow of urine. Therefore, we believe tension sutures which are placed through the perineum are preferable to the use of the bag catheter to produce tension.

DR. REED M. NESBIT (Ann Arbor, Mich.): I would like to ask Dr. Campbell a question. He stresses the importance of avoiding traumatic manipulation. How does he avoid it when in the preliminary part of the operation he separates the seminal vesicles from the rectum? Isn't that traumatic in his hands?

DR. BEN D. MASSEY (Pasadena, Cal.): I wish to thank the discussants very much. At least they have generated a little interest.

My whole point in presenting this paper was that I would like to see some laboratory work done on regeneration and reanastomosis, and on the viability of bladder mucous membrane.

I think any procedure in which part of an organ is removed, such as the bladder, that has a carcinoma with a multicentric focus of origin, is open to some question. As you noticed, I limited it to the single infiltrating tumors within an otherwise normal bladder. I believe other procedures should apply when we have multiple foci of carcinoma.

I have seen many cystectomies at which I have been appalled because, in the hands of many urologists, the skinning out of the bladder is called a cystectomy for treatment of carcinoma. I think many extensive segmental resections, which take the full thickness and extend widely, remove the local point of cancer as rapidly as cystectomy.

When there is any question of palliation, I think one can cure the cancer locally as readily by extensive segmental resections in selected cases as one can by urinary diversion procedures.

Thank you very much.

DR. EDWARD W. CAMPBELL (Philadelphia, Pa.): Dr. Flocks mentioned the work which he did with serum acid phosphatase estimations. I included this in a previous paper, and thought it might suggest a mechanism for the transfer of malignant cells into the bloodstream. I have discarded the idea for more substantial evidence for this discussion.

Cole has shown in his recent work that the use of antibiotics during the operative procedure (most of which was in colo-rectal cancer) substantially reduces the number of liberated malignant cells in the bloodstream during the surgical procedure. This may be a useful suggestion.

Dr. Hinman raised the question of diagnosis. I have talked with men across the country, and I know a great many who operate on carcinoma of the prostate gland without doing a preliminary biopsy. I do not condone this. We have used needle biopsies for diagnosis, frequently without success. I think this method is very traumatic, and generally unreliable. Open perineal biopsy is the most reliable approach for diagnosis. This requires retraction and manipulation of malignant tissue to mobilize the posterior wall of the prostate gland, but when one is faced with a problem of making an accurate diagnosis, what else can one do?

A problem, with regard to cancer of the prostate gland, is our inability to predetermine the extent of the lesion by the size of the lesion

palpated rectally. In many cases we have noted an apparent isolated lesion by rectal palpation, but when the gland was examined following removal, the carcinoma was found to involve a large portion of one or both lobes.

We do perineal biopsies on these people as carefully as we can. If a small isolated lesion is found near the apex of the prostate gland, we perform a total perineal prostatectomy. However, all growths which are near the base, or are not strictly isolated should be removed by the method described in this paper, because it is less traumatic, and minimizes the possibility of dissemination of cancer cells.

Dr. Baker mentioned the use of a bag. I purposely use a catheter which is distended with 25 cc of water. I believe this is less liable to press on the ureters. It is much more comfortable and drains better than a bag, because the tip of the catheter is lower in the bladder. Anuria has not occurred in our patients.

Dr. Nesbit questioned whether dissecting the seminal vesicles was traumatic. I do not think so. We start at the apex, pick up the vessel first. A Kelly clip is applied to the vessels and used for traction to gently lift the seminal vesicles, and gently tease them away from the rectum with blunt forceps. When these vessels are closed, I think there is no probability of extension. All vessels are closed before the seminal vesicles are manipulated.

Do I have time to add a little support to Dr. Massey's comments? I had a case similar to Dr. Massey's with a transitional cell carcinoma at the vesical outlet on the right side. This was six years ago. The bladder was entered anteriorly, as I have shown in my illustrations, and the entire trigone resected on the right side. Approximately three-fourths of the trigone and a large section of the bladder with the right intramural ureter were removed. The ureter was transplanted to a higher level in the posterior wall. The prostate and seminal vesicles were removed and the bladder anastomosed to the urethra with 4 interupted sutures.

[Slide] This slide presents an intravenous urogram made in October 1957, over five years from the time the patient was operated on. There is excellent bilateral function and no ureteral or pelvic dilatation on the right or transplanted side. It will be six years in June since he was initially operated on, and this is a postoperative x-ray showing the good function on the remaining side.

I might add support to Dr. Cordonnier's comment because this patient had incontinence when on his feet and required an urethral clamp. About one year ago hematuria and urethral bleeding developed. The patient was found to have a transitional cell carcinoma of the urethra at the site of application of the clamp. The involved section of the urethra was resected and the urethra anastomosed.

The patient is now about 73 years old. Since the urethral growth was resected, he has been completely continent.

TUMORS OF THE TESTIS

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This paper deals with an analytical study of 510 cases of testis tumor seen at the Walter Reed Army Hospital from January 1, 1940 through December 1956. The project was initiated primarily to evaluate the results of therapy. To the best of our knowledge the 510 cases represent the total number seen during this period. A long term followup was obtained in 490 or 96.1 per cent. The five-year survival group includes all the cases observed between January 1940 and December 1952, with the followup extending to December 1957.

In reviewing any large series of cases, it is quite easy, both from the author's and reader's standpoint, to become involved in a hopeless maze of figures. An effort has been made to reduce the statistics to as simple and understandable a form as possible consistent with an accurate report. It is also the desire of the authors to present the data in an unbiased manner. In an effort to insure accuracy, a statistician was employed.

From time to time, reports have appeared in the literature by various authors, based on a part of this series. These will be listed as references but will not be discussed for comparison. Likewise, it does not seem practical to attempt to compare the results in this series with those from other clinics. There are too many factors involved to permit valid conclusions.

The average age in the 510 patients was 27.9 years. The youngest patient was 3 years old and the oldest was 57. Seminoma occurred more frequently in somewhat older individuals with an average of 30.7 years. Embryonal carcinoma and teratocarcinoma occurred at an average of 26.1 and 26.6 years respectively. The tumor appeared in a cryptorchid testis in 26 instances or 5.1 per cent (1 in 19). Six of these had had a previous orchiopexy.

Distribution of the 510 tumors into types is as follows: seminoma, 191 cases or 37.4 per cent; embryonal carcinoma, 157 or 30.8 per cent; teratocarcinoma, 128 or 25.1 per cent; and miscellaneous, 34 or 6.7 per cent. Included in the miscellaneous group are the cases of adult teratoma, choriocarcinoma, interstitial cell tumor and other rare types.

The study of this series has brought out several interesting facts and observations which deserve mention.

1) A longer followup than 5 years has very little significance. Of the 180 patients who died from tumor, only two lived more than 5 years. Both were teratocarcinoma and both died in the sixth year. Most of the deaths occurred within 2 years.

2) There were 4 cases of bilateral tumor. One of these was an interstitial cell tumor which occurred in both testes simultaneously. Bilateral orchiectomy was performed, followed by irradiation, and the patient is living more than 4 years. Two patients had bilateral seminoma. In one of these the tumors occurred at an interval of 2 years, and in the other within the same year. The fourth patient had a teratocarcinoma in 1943 treated by orchiectomy and lymphadenectomy. Two years later a seminoma developed in the opposite testis which was likewise treated by radical surgery. These last three patients also received irradiation therapy and are living and well more than 5 years.

3) In 2 patients with tumor of the testis osteogenic sarcoma developed, attributed to irradiation. One had 7600 r and the other only 2900 r, delivered to the abdomen. Both died of their sarcoma after 5 and 7 years respectively.

4) There were 3 cases of teratocarcinoma in which lobectomy was performed for lung metastases and all are living and well; two living more than 6 years and one more than 5 years. Two of these patients had a solitary nodule in the lung and the other had 3 areas of metastasis confined to one lobe.

5) In the seminoma group (191 cases), 23 were described pathologically as anaplastic seminoma. Three of these died of metastasis; one died of seminoma, one from embryonal carcinoma and the other choriocarcinoma.

6) There was one death from adult teratoma

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and autopsy revealed the metastases to be choriocarcinoma. In a recent case of teratoma not included in this series, the nodes removed on lymphadenectomy proved to be teratocarcinoma.

7) One patient with choriocarcinoma is living and well after 8 years. He was treated by orchiectomy and lymphadenectomy, however the nodes removed were all negative.

8) There is one patient with embryonal carcinoma treated by radical lymphadenectomy without radiation, in whom the nodes were positive, and who is living and well over 8 years. To the best of our knowledge, this is the first such case reported in the literature.

METASTASIS ON ADMISSION

Seventy-one or 13.9 per cent of the 510 cases had demonstrable metastasis on admission, as determined by physical examination, x-ray or urographic study. Five of the 13 patients in the seminoma group responded well to irradiation and are living 5 to 13 years following treatment. None of the 50 patients with embryonal or teratocarcinoma, however, have survived their disease except one, and he has been followed for only one year.

INOPERABLE ON ADMISSION

Forty-eight patients (9.4 per cent) showed no clinical evidence of metastasis on admission, but on attempted lymphadenectomy were found to be inoperable. All were treated by orchiectomy and irradiation. Four of the 5 patients in the seminoma group are well 5 to 13 years. Only four of the 41 patients in the radioresistant group (embryonal carcinoma and teratocarcinoma) are living and these have been followed less than one year.

If we add these figures to those in the previous section we find 119 patients or 23.3 per cent, who had demonstrable or inoperable metastases when first seen. The over-all mortality for the 119 patients was over 92 per cent. With the present methods of treatment, no hope can be offered any of these unfortunate individuals except those with seminoma. These figures emphasize the urgent need for earlier diagnosis.

TYPE OF TREATMENT AND RESULTS

Five patients in the total series of 510 cases were considered terminal and no treatment was prescribed. Another five received palliative irradiation only. Simple orchiectomy was performed in 16 patients; 186 were treated by orchiectomy and irradiation; 29 had orchiectomy and lymphadenectomy with no irradiation; and 269 were treated by combined orchiectomy, lymphadenectomy and irradiation. Three hundred and ninety-six of the total series fall in the five-year group and 389 of these have adequate followup. The five-year survival rate is shown in table 1. Sixty-one per cent have survived for 5 to 15 years or have died from other causes. The survival rate for those patients with seminoma was 92 per cent; for those with embryonal carcinoma, 44 per cent; for those with teratocarcinoma, 44.7 per cent; and for those in the miscellaneous group, 47.8 per cent.

Orchiectomy and irradiation. The value of irradiation therapy in the treatment of seminoma of the testis is well known. One can expect a cure in approximately 95 per cent by treatment with orchiectomy and irradiation alone, applied in a dosage of 2000 r. Lymphadenectomy is unnecessary and need not be considered except possibly in those cases in which the microscopic sections show marked anaplasia, and the diagnosis may be in doubt. Embryonal carcinoma and teratocarcinoma are highly radioresistant. Although irradiation should be included in the treatment of these tumors, its value is difficult to assess. The morbidity associated with the application of large dosages of x-ray may be considerable and complications with late sequelae are not infrequent. As applied to the treatment of the radioresistant tumors, it must be considered in the realm of radical therapy.

The results of treatment by orchiectomy and irradiation are shown in table 2. The five-year survival rate in embryonal carcinoma and teratocarcinoma is 13 per cent and 17.7 per cent respectively. These figures are low but it must be remembered that this group includes many patients with known metastasis. None of the patients in the radioresistant group, however, who had metastasis on admission or were found to have inoperable nodes responded to irradiation and all died within two years.

Lymphadenectomy without irradiation. There were 29 patients treated by orchiectomy and lymphadenectomy in which no irradiation was given. A followup was obtained in 24. The group is small but significant in that one patient had an embryonal carcinoma with positive nodes and is

living 8 years after treatment. Sixteen of these patients are included in the five-year group in the next section and will not be discussed here.

Orchiectomy, lymphadenectomy and irradiation. This group comprises all the patients treated by lymphadenectomy, and the results are shown in table 3. All received irradiation but 16. The five-year survival rate for the total group was 79.4 per cent. For those patients with seminoma, the survival rate was 96 per cent; for those with embryonal carcinoma, 72.3 per cent; for those with teratocarcinoma, 60.6 per cent; and for those in the miscellaneous group, 83.3 per cent. Table 4 shows the survival rate in the patients who had positive nodes. For those patients with embryonal carcinoma, the survival rate was 65 per cent and for those with teratocarcinoma, 30 per cent.

It is interesting to note that while no patient with embryonal carcinoma or teratocarcinoma who had metastasis on admission, and was treated by orchiectomy and irradiation, survived his disease, 19 of the 40 patients in these two groups with positive nodes on lymphadenectomy lived more than 5 years, or 47.5 per cent. Sixteen of these are living and well from 5 to 13 years; three died from other causes (2 after 7 years and 1 after 1 year) and autopsy revealed no evidence of tumor. Of these 19 cases, 13 were embryonal carcinoma and 6 teratocarcinoma.

TABLE 1. *Five-year survival; total cases (389 cases followed)*

Type of Tumor	No.	Alive	Dead			Alive or Dead Without Tumor	
			Total	From tumor	Other causes	Total	Per cent
Total	389	204	185	150	35	239	61.4
Seminoma	138	103	35	11	24	127	92.0
Emb. ca.	125	48	77	70	7	55	44.0
Teratoca.	103	42	61	57	4	46	44.7
Misc.	23	11	12	12	0	11	47.8

TABLE 2. *Five-year survival; treated by orchiectomy and radiation (127 cases followed)*

Type of Tumor	No.	Alive	Dead			Alive or Dead Without Tumor	
			Total	From tumor	Other cause	Total	Per cent
Total	127	31	96	82	14	45	35.4
Seminoma	36	20	16	5	11	31	86.1
Emb. ca.	54	4	50	47	3	7	13.0
Teratoca.	34	6	28	28	0	6	17.7
Misc.	3	1	2	2	0	1	33.3

TABLE 3. *Five-year survival; treated by orchiectomy and lymphadenectomy (all had radiation except 16) (243 cases followed)*

Type of Tumor	No.	Alive	Dead			Alive or Dead Without Tumor	
			Total	From tumor	Other cause	Total	Per cent
Total	243	172	71	50	21	193	79.4
Seminoma	100	83	17	4	13	96	96.0
Emb. ca.	65	43	22	18	4	47	72.3
Teratoca.	66	36	30	26	4	40	60.6
Misc.	12	10	2	2	0	10	83.3

TABLE 4. *Five-year survival; lymphadenectomy; positive nodes*

Type of Tumor	No.	Alive	Dead			Alive or Dead Without Tumor	
			Total	From tumor	Other cause	Total	Per cent
Total	51	24	27	24	3	27	52.9
Seminoma	11	8	3	3	0	8	72.7
Emb. ca.	20	11*	9	7	2	13	65.0
Teratoca.	20	5†	15	14	1	6	30.0
Misc.	0	0	0	0	0		

* Alive 12, 12, 12, 11, 11, 8, 5, 5, 5, 5 and 5 years.
† Alive 13, 13, 12, 7 and 5 years.

There were 192 patients with negative nodes in the five-year survival group and of these 26, or 13.5 per cent, died from their tumor. This may be explained by three possibilities: 1) there was undetected distant metastasis present prior to surgery, 2) there was contralateral involvement of the retroperitoneal nodes, or 3) the lymphadenectomy on the affected side was inadequate. During the period covered by this report, resection of the retroperitoneal lymph channels was limited to the affected side. Since 1954, bilateral lymphadenectomy has been performed routinely. Contralateral involvement of the nodes has been observed not infrequently. During the past year there were 3 such cases in a total of 19 dissections. It will be interesting to see if a future study of this group shows any improvement in the survival rate.

SUGGESTED TREATMENT OF TESTIS TUMORS

The management of tumors of the testis is by no means a settled issue. Surgery and the x-ray have improved the outlook for many of these unfortunate individuals but the results to date still leave much to be desired. Undoubtedly there is still room for improvement in surgical technique and application of irradiation. The field of chemistry offers some hope but as yet is not well explored. On the basis of our present knowledge and experience, the current policy for treatment of testis tumors at the Walter Reed Army Hospital is as follows.

1) *Seminoma.* If there is no evidence of clinical metastasis, the orchiectomy is followed by irradiation therapy to the abdominal lymphatic chain. This consists of giving a total tumor dose of 2000 r. through opposing portals over an average period of 28 days. If metastases are clinically present in the abdomen, mediastinum, and/or the clavicular areas, irradiation therapy is then directed to the entire lymphatic chain, giving a total tumor dose of 2000 r. to each area. This can usually be given in an average period of 50 days. If there are metastases to the lung, these areas are included in the radiation field.

2) *Embryonal carcinoma and teratocarcinoma.* In the absence of clinical metastasis, orchiectomy is followed by bilateral lymphadenectomy performed through a transperitoneal approach. If the nodes removed are negative pathologically no further therapy, such as irradiation, is given. If any of the nodes removed reveal metastasis, or if at the time of surgery the patient was found to be inoperable and only a biopsy could be obtained, postoperative irradiation is applied to the entire lymphatic chain, including the left supraclavicular area, mediastinum and abdomen. A tumor dose of 4000 r. is delivered to each of these areas over an average period of 110 days, beginning with the upper abdominal portal. An exposure of 4000 r. is considered the upper limit of safety. All irradiation is given by the million volt therapy equipment. If clinical evidence of metastasis is present prior to treatment, orchiectomy is followed by irradiation applied to the entire lymphatic chain, and will include the lung fields if involved. Treatment in these advanced cases, or in those patients who return with metastasis, unfortunately may be limited to palliative measures. These include nitrogen mustard therapy with ACTH, castration with or without supplemental stilbestrol, local irradiation and other measures.

3) *Choriocarcinoma.* Patients with choriocarcinoma are treated by high orchiectomy only. It is felt that lymphadenectomy and/or irradiation therapy will not alter the course of the disease. Other supplemental measures have likewise proven unsatisfactory.

4) *Adult teratoma.* These patients are treated by orchiectomy and lymphadenectomy, followed by irradiation if the nodes are positive. Radical treatment is considered justifiable because of the minimal surgical risk associated with lymphadenectomy and the incidence of metastasis by elements other than teratoma. There is one such case in this series, and a recent patient had positive nodes showing teratocarcinoma.

SUMMARY

A study of 510 cases of testis tumor is reported with a suggested plan of treatment.

The authors acknowledge the invaluable assistance of Benjamin L. Parnell, chief, Statistical Analysis Unit, Professional Records Branch, Armed Forces Institute of Pathology, in the analysis of the data.

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RETROPERITONEAL LYMPH NODE DISSECTION FOR TESTICULAR TUMORS

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Tumors of germinal cell origin comprise 96½ per cent of all testicular tumors (Dixon and Moore). In considering these tumors it is of fundamental importance to realize that they arise from totipotent sex germ cells and have within them the potential ability to give rise to any tissue of the body from the simple to the most complex mixed neoplastic teratoid growth (Moore). Thus basically they are mixed tumors and frequently do not fit into any standard histological pattern or type.

Therefore it is no wonder that their classification has been extremely difficult and that, in the past, various different classifications have been advocated. However, in recent years several large series of such tumors have been studied by various investigators (Friedman and Moore) who have come to basic agreement on their classification, partly on the basis of their clinical behavior and partly on the basis of their histological pattern.

While chorioepithelioma commonly, and other tumors on occasion, metastasize via the blood stream, the usual metastases of testicular tumors are to lymph nodes. It has been shown that the lymphatics draining the testis accompany the internal spermatic vessels, running upward in the cord through the inguinal canal, and then retroperitoneally along the lateral and anterior surface of the aorta and inferior vena cava to the region where the spermatic arteries arise from the aorta, and the internal spermatic vein joins the inferior vena cava on the right and the renal vein on the left. In this region of the renal vascular pedicles and below, along the aorta and vena cava, are located the lymph nodes where the first lymphatic metastases from testicular tumors occur (Hinman, '14 and '19; Cooper, Leadbetter and Chute) (fig. 1). Although the early metastases from tumors of the right testis tend to keep to the right of the midline along the vena cava, and those from tumors of the left testis tend to keep to the left along the aorta, it is not too uncommon for fairly early metastases to cross over to the opposite side. After this area of primary metastases has become heavily loaded with tumor emboli, secondary metastases then spread upward and/or across the midline to the opposite side and/or retrograde down to the iliac vessels. After these secondary metastases have occurred, surgery is usually of no avail. Therefore, the purpose and hope of radical orchiectomy with retroperitoneal lymph node dissection is to remove the testicular tumor together with its site of primary lymphatic metastases before the disease has spread beyond this zone.

Radical orchiectomy with dissection of the retroperitoneal lymph nodes was first described in the U.S.A. by Hinman in 1914. Although Hugh Young used it in a few cases, despite Hinman's advocacy it was employed but little until Kimbrough at Walter Reed Army Hospital started using it a number of years ago. Stimulated by Kimbrough, Lloyd Lewis became a strong advocate, and in 1948 reported 250 cases of testicular tumor with 192 retroperitoneal dissections. Others have taken it up, and by now it is the general opinion that this procedure in combination with x-ray therapy gives a better rate of cure and survival in cases of certain testicular tumors than does x-ray alone. For example, recently Staubitz and associates at the Roswell Park Memorial Institute in Buffalo compared the results in a series of cases of embryonal carcinoma and teratocarcinoma treated by node dissection via a thoracoabdominal incision in combination with x-ray therapy with a similar earlier series of cases at the same hospital treated by x-ray therapy alone reported by Sauer and associates. Staubitz and his co-workers after careful comparison came to the conclusion that the combination of irradiation and surgery had resulted in a definite improvement in the cure and survival rate over that conferred by irradiation alone in the earlier series. Others, including Cahill, Dean, and Leadbetter, hold this same opinion.

The testicular tumor which most frequently is "pure", i.e. composed entirely of cells of one histological pattern, is the seminoma. This is an extremely radiosensitive tumor, and it is now generally agreed that, if the diagnosis of "pure

seminoma has been made on a testis removed by orchiectomy, the indicated subsequent treatment is not surgery but x-ray therapy, either prophylactic to the zone of primary metastasis, or therapeutic to metastases which have already occurred. This method of treatment has produced a high percentage of cures.

The treatment of true chorioepithelioma seems well nigh hopeless at the present time, as this tumor grows rapidly, metastasizes viciously and widely by the bloodstream, is not radiosensitive, and almost always progresses swiftly to a fatal termination. Therefore surgery is not recommended, and little may be expected from x-ray therapy, although it can be given a trial.

Neither so easily curable as the radiosensitive "pure" seminoma nor so hopeless as the fatal true chorioepithelioma, is the group made up of embryonal carcinoma, teratocarcinoma and teratoma, which comprises about 60 per cent of all testicular tumors. As mentioned previously, these tumors are very apt to be mixed. Adult teratoma is apt to contain elements of malignant cell groups and thereby form teratocarcinoma—and teratoid elements may occur in any combination with seminoma and/or embryonal carcinoma and/or chorioepithelioma. Embryonal carcinoma is often associated with seminoma. Thus any combination can and frequently does occur. This accounts for the fact that the metastases from a primary tumor predominantly of one cell type, sometimes evidence predominance of a different cell type—the more malignant cell elements having metastasized, while the less malignant ones have not. Some of these elements, notably the teratomatous, are radioresistant while others are radiosensitive.

No chain is stronger than its weakest link, and no tumor is less malignant than its most malignant component. With mixed tumors, some of whose elements are radiosensitive and some radioresistant, the combination of retroperitoneal lymph node dissection plus supervoltage x-ray therapy seems to be the most effective treatment, as has been shown by Staubitz and associates. The surgical removal of those retroperitoneal lymph nodes which are the site of the primary metastases should best eradicate the radioresistant elements, while supervoltage x-ray therapy is aimed to take care of radiosensitive elements as well as any stragglers that have escaped surgical removal. This has been our

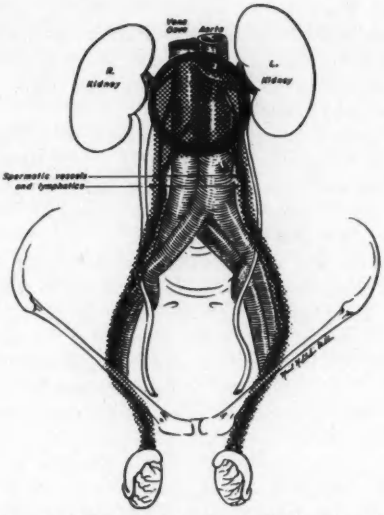

FIG. 1. Schematic anatomical drawing indicates lymphatics of testes (stippled area) that accompany spermatic vessels to primary site of earliest lymph node metastases from testes (inside circle between kidneys).

procedure in dealing with the embryonal carcinoma-teratocarcinoma-teratoma group. It would have made a better control in order to test the efficacy of retroperitoneal node dissection alone not to have given any x-ray therapy after the surgery, but our policy has been to do everything possible to cure the patient. Of course, in the presence of widespread metastases, surgery is not carried out, and x-ray therapy is limited to palliation for pain.

The cases of all patients with testicular tumors of germinal cell origin seen and treated at the West Roxbury (Massachusetts) Veterans Administration Hospital from December 1946 through June 1953, and then at the Boston Veterans Administration Hospital from July 1953 through June 1957, have been reviewed and studied. The cases of 105 patients were reviewed but only 76 were included in this study, as the available data on the others were insufficient. The rejected cases mostly were of patients seen early in this series who had been operated upon in one of the armed services, and who later entered our Veterans Hospital for palliative x-ray therapy or terminal care.

One of the purposes of this study was to evaluate the worth of retroperitoneal lymph

node dissection in dealing with the embryonal carcinoma-teratocarcinoma-teratoma group. As previously stated, this procedure was seldom employed by us when dealing with chorioepithelioma or pure seminoma.

Between January 1949 and June 1957, 26 patients (approximately one-third of the 76 cases in our series) underwent 32 surgical explorations for retroperitoneal lymph node dissection (6 bilateral dissections).

In our first two cases the node dissections were first performed through the flank incision used by Hinman, Kimbrough and Lloyd Lewis. Through this incision the exposure of the region above the renal pedicle was not satisfactory, so both these cases were re-explored shortly thereafter through a thoracoabdominal incision. The exposure of the region above the pedicle was much better, the dissection was easier and safer, and in each instance a malignant node which had not been reached through the earlier flank incision was discovered and removed. A third patient upon whom a node dissection had been performed elsewhere through a Hinman type flank incision was re-explored by us through a thoracoabdominal incision, and again a positive node above the renal pedicle was found and removed. Two of these three patients—one of whom had embryonal carcinoma and the other teratocarcinoma with elements of chorioepithelioma—are now living and apparently free of disease after 9 years and 3 months, and 6 years and 4 months respectively. The third patient, who had embryonal carcinoma, died 2½ years later of chest metastases, but autopsy showed no residual malignancy in the retroperitoneal area. Whether the absence of disease in the retroperitoneum in this patient was due to the surgical dissection or whether the moderate amount of x-ray therapy which he received would have eradicated any metastases, if present, is problematical. However, it seems quite possible that the eradication was achieved by the surgery. These three cases, which enabled us to make a comparison of these two types of incision in the same cases, made a deep impression on us, as they definitely and conclusively demonstrated the superiority of the thoracoabdominal incision over the Hinman type of incision. Therefore the thoracoabdominal incision, as reported by Cooper, Leadbetter and Chute, was used in all our retroperitoneal node dissections.

Seven of these 26 patients had inoperable disease found at operation, and died of their disease in from 2 to 10 months.

Eight patients had retroperitoneal dissections but no disease was found in the removed nodes. However, two of these died of their malignancy 2 years after their surgery. One of these two died of metastatic chorioepithelioma which had not been detected in either the primary testicular tumor or in the removed nodes, while the other who had mixed teratocarcinoma and chorioepithelioma of the testicular tumor died of extensive metastases to the retroperitoneum, liver, lungs, and vertebrae. The remaining six patients are living and apparently free of disease for the following periods of time after surgery respectively—2 years, 3 years, 4 years, 5 years, 6 years, 6 years. The predominating histological types in these six were: teratoma (3 cases), adult teratoma, embryonal carcinoma, and seminoma (1 case each).

In the remaining 11 of these 26 patients nodal metastases were found and removed by retroperitoneal dissection, and it is in this group that the results of surgery are most significant. Four of these patients died of their disease in from 5 months to 2½ years, but the other 7 are still living and apparently free of disease for the following periods of time after operation respectively: 9 years, 9 years, 7 years, 6 years, 5 years, 3 years, 2 years—the average time being 6 years. The predominating histological types in these 7 survivors were: embryonal carcinoma (3 cases), teratocarcinoma (3 cases), seminoma (1 case). None of these 7 "cured" cases gave evidence at operation of disease extending across the midline to involve nodes on the opposite side. Two of them had bilateral node dissection, but no disease was found in the nodes on the opposite side. Of these 7 cases, all but one, who has gone 5 years without evidence of recurrence, had postoperative x-ray therapy. As previously stated, this makes it hard to evaluate the respective value of the node dissection and of the x-ray therapy. However, 3 of these patients had teratocarcinoma, which is usually very radio-resistant, so it appears as if at the least some share of the credit should go to the surgery.

Six patients had bilateral retroperitoneal node dissections. Three of these are living and well 5 years and 8 months, 5 years, and 3 years, respectively. The first of these showed no disease in any of the retroperitoneal tissue dissected, whi

the second and third showed disease only on the same side as the testis. The other three patients died of their disease. One of these had a lot of disease on the same side as the testis, while the other two had bilateral disease and developed chest metastases.

Involvement of nodes in the region of the renal pedicle on the opposite side from that of the testicular tumor is not common except when the disease is in an advanced inoperable state. However, it has been known to occur early, and this possibility must always be kept in mind. In our opinion bilateral retroperitoneal node dissection must be seriously considered in the case of any tumor except "pure" seminoma or chorioepithelioma, unless there is evidence of inoperable or multiple distant metastases, or unless all nodes removed at the retroperitoneal operation on the same side as the testicular tumor prove to be negative microscopically and, in addition, careful palpation through the deliberately opened peritoneum at the time of node dissection reveals nothing at all suspicious of disease at, above, or below the region of the renal pedicle on the opposite side.

It is our opinion that retroperitoneal node dissection in addition to x-ray therapy has given additional benefit in just those cases where it would be expected to do this; i.e., in the less radiosensitive embryonal carcinoma-teratoma-teratocarcinoma group where metastases were found and removed. Seven out of 11 patients (64 per cent) are living for an average of 6 years following thoracoabdominal resection of involved retroperitoneal nodes combined with deep x-ray therapy. This compares favorably with a similar group treated similarly by retroperitoneal node dissection and deep x-ray therapy where another author reported 46 per cent living for at least 5 years (Lewis, '53). Although our group is smaller (by 11 to 28) than the other group, our better survival figures (64 per cent to 46 per cent) can probably be ascribed to the fact that all of our cases were done through the thoracoabdominal incision, the demonstrated superiority of which has already been referred to, while the flank approach was used in the other group.

In our series of 32 retroperitoneal node dissections there were no postoperative deaths, and also no radiation deaths. The most serious postoperative complication was a mild case of lower nephron nephrosis, thought to be due to a transfusion of mismatched blood, which cleared up in only a few days. Three cases required postoperative needle aspiration of bloody fluid from the pleural cavity. Two cases had unexpected nephrectomy performed at the time of the retroperitoneal node dissection. In one of these cases, tumor involved the kidney pedicle so intimately that it was felt that the only hope of eradicating all the tumor was to remove the kidney. In the other case the renal artery was accidentally traumatized during the dissection about the pedicle necessitating nephrectomy.

To turn to another phase of this problem: We were quite impressed by our inability to determine by external abdominal examination (Young and Davis) or by x-rays the presence or absence or extent of retroperitoneal metastases. In the region of the renal pedicle it is impossible to feel metastases unless the metastatic mass is extensive and the patient is thin. Not infrequently extensive retroperitoneal metastases will displace the kidney or one or both ureters laterally and may even obstruct them, in which case their presence may be revealed by intravenous urography or retroperitoneal pneumography (fig. 2). However, 33 per cent of those with gross retro-

FIG. 2. X-ray shows left ureter and kidney displaced laterally by extensive inoperable retroperitoneal metastases from embryonal carcinoma of left testis. Left psoas muscle shadow is obliterated by retroperitoneal disease which also prevents air of retroperitoneal pneumogram from getting into retroperitoneal area on left.

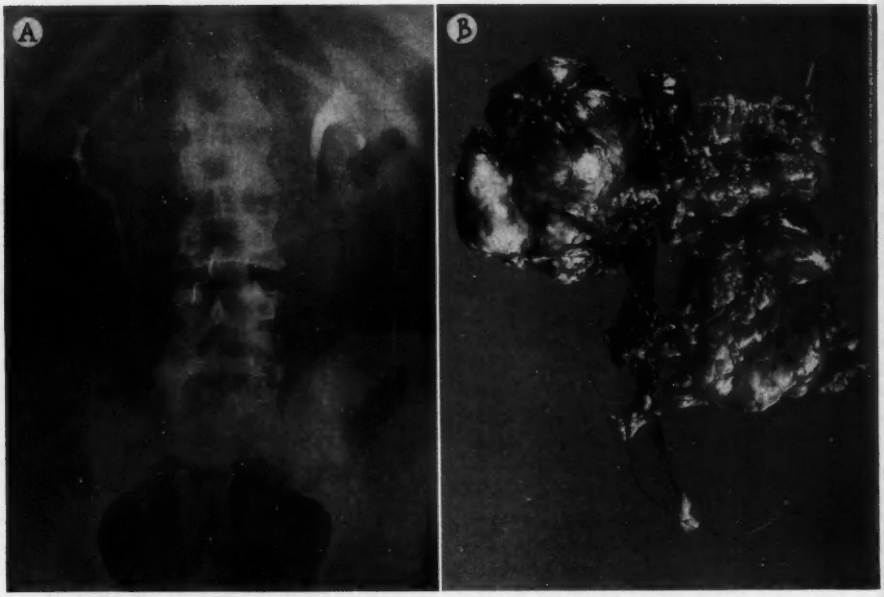

FIG. 3. *A*, essentially normal intravenous pyelogram with clear psoas muscle shadow in patient with extensive retroperitoneal metastases from teratocarcinoma of right testis. Mass was removed (see *B*). *B*, mass of lymph nodes involved by metastatic teratocarcinoma (weight 335 gm.) removed by right thoracoabdominal retroperitoneal dissection from patient whose essentially normal intravenous pyelogram is shown in *A*. This indicates how x-rays may fail to reveal retroperitoneal metastases.

peritoneal metastases had no palpable mass in the abdomen or flank and had normal intravenous urograms (fig. 3). An additional 26 per cent had only a questionably felt abdominal or flank mass, and had normal intravenous urograms. Thus abdominal palpation and intravenous urography failed to definitely reveal the presence of gross retroperitoneal metastases in more than half (59 per cent) of the cases where they existed.

To help solve this problem by getting early and more accurate information about the presence or absence of gross retroperitoneal metastases and, if they are present, of their probable operability, in recent cases we have been carrying out a limited abdominal exploration at the time of the initial orchiectomy. (Our policy is to perform orchiectomy initially, and to await the result of the microscopic study of the permanent sections before proceeding with the retroperitoneal node dissection). This exploration is done through an upward extension of the orchiectomy incision, and has not added any appreciable or unwarranted additional risk or morbidity to the operation. Through this incision, the liver, and the region of the renal pedicles and the anterior surface of the aorta and vena cava below this region are very carefully palpated to detect if enlarged hard nodes or a large mass is present. If nodes are found, careful note is made as to their position and as to whether they are bilateral. If a mass is found, it is carefully palpated to determine its extent and whether it is probably removable or not. We feel that this procedure has given us information which is very valuable in planning the treatment of the case, especially in regard to subsequent retroperitoneal node dissection. For, if a hard fixed mass, obviously inoperable, is found, retroperitoneal node dissection will not be attempted, and the patient will be spared this futile major operation. Out of the 26 patients in our series who underwent retroperitoneal operation in the hope of removing metastases limited to the primary zone of nodes, seven or 27 per cent were found at operation to have extensive inoperable disease. Most of these futile operations could have been prevented by limited exploration at the time of orchiectomy, which in the future should save many of those

with inoperable disease from a subsequent major operation doomed to failure before its start. Furthermore, the diagnosis of inoperability is made with a minimum of delay, and the location of the disease more accurately known in order to administer the optimum treatment with supervoltage x-ray therapy without delay. Therefore, we now have adopted this limited exploration at

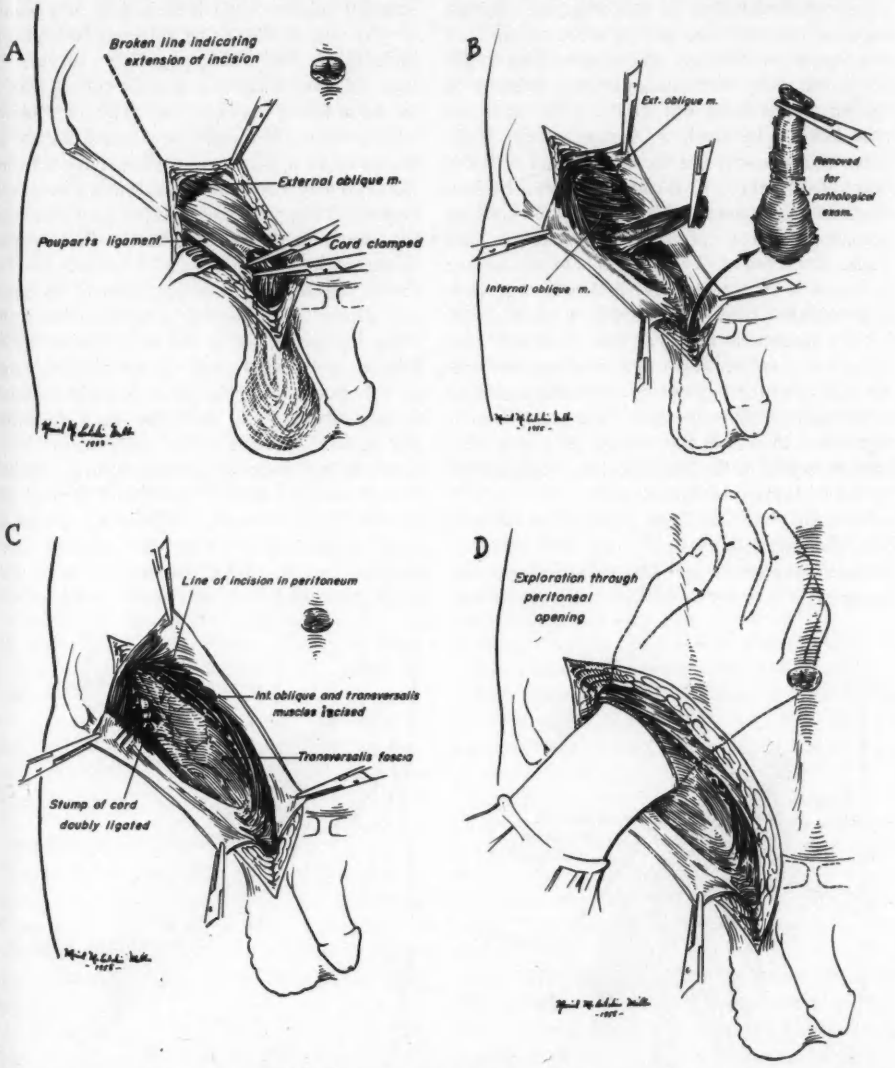

FIG. 4. *A*, spermatic cord doubly clamped at its exit from external inguinal ring before freeing up testis. Broken line indicates how incision will be extended upward. *B*, testis removed for immediate examination by pathologist. External oblique fascia has been opened exposing inguinal canal. Cord freed up to internal inguinal ring. External oblique muscle split upward above internal ring. *C*, internal oblique and transversalis muscles divided for about 5 inches above internal inguinal ring exposing peritoneum beneath. Dotted line indicates where peritoneum will be opened. Cord freed up as far retroperitoneally as feasible and stump doubly ligated. Ends of ligatures left at least 1 inch long to facilitate future identification of end of cord on retroperitoneal dissection. *D*, hand introduced through opening in peritoneum palpating primary zone of lymph node metastases along inferior vena cava and aorta and in region of kidney pedicles.

the time of orchiectomy as standard operating procedure in all cases of testicular tumor.

The procedure is carried out as follows: At the time of orchiectomy, the spermatic cord is exposed and isolated at its exit from the external inguinal ring and clamped in order to shut off the escape route of any metastases which might be liberated by the manipulations incident to freeing up the testis (fig. 4, *A*). If tumor is unmistakable, the cord is clamped with Kelly hemostats. However, if the existence of tumor is questionable, the cord is clamped with a rubber-shod intestinal clamp which will do the cord no permanent damage after it is taken off, in case tumor is not found. If doubt exists as to whether or not it is tumor, it is far better to remove a nonmalignant testis than to take a chance and leave a malignant testis, as that may well cost the patient his life. Biopsy of a suspected testis on the table is absolutely never to be done, and is to be unequivocably condemned. The authors have seen cases in which the biopsy of a testicular tumor resulted in the implantation of cells in the wound with eventual fatal results.

After the cord has been clamped at its exit from the external inguinal ring, the incision is extended downward and the testis is freed up, taking great care not to cut into it, and removing en bloc with the testis any portions of scrotum or tunica which are adherent to it. If tumor is found, the cord is cut between clamps and the ends carbolized as in an appendectomy. Now the external oblique fascia is incised as in a herniorrhaphy (fig. 4, *B*) taking care not to injure the ilioinguinal and iliohypogastric nerves, the inguinal canal is opened, and the cord is freed up to the internal inguinal ring. Then the oblique and transversalis muscles are incised for about 5 inches in an upward and slightly outward direction. (In case a retroperitoneal node dissection is performed later, this incision can be continued in the same direction as a tenth rib interspace thoracoabdominal incision.) The vas is freed up at the internal inguinal ring, ligated, sectioned, and allowed to go its way down into the pelvis. Then the remainder of the cord containing the internal spermatic vessels and lymphatics is freed up retroperitoneally as far as feasible, clamped, doubly ligated, cut, and the ends carbolized (fig. 4, *C*). The ends of the ligatures are left at least one inch long to facilitate future identification of the end of the cord. Now through this incision the peritoneum is deliberately opened, the hand inserted (fig. 4, *D*) and the liver, the area of the renal pedicles and above, the anterior surface of the aorta and vena cava down to the bifurca-

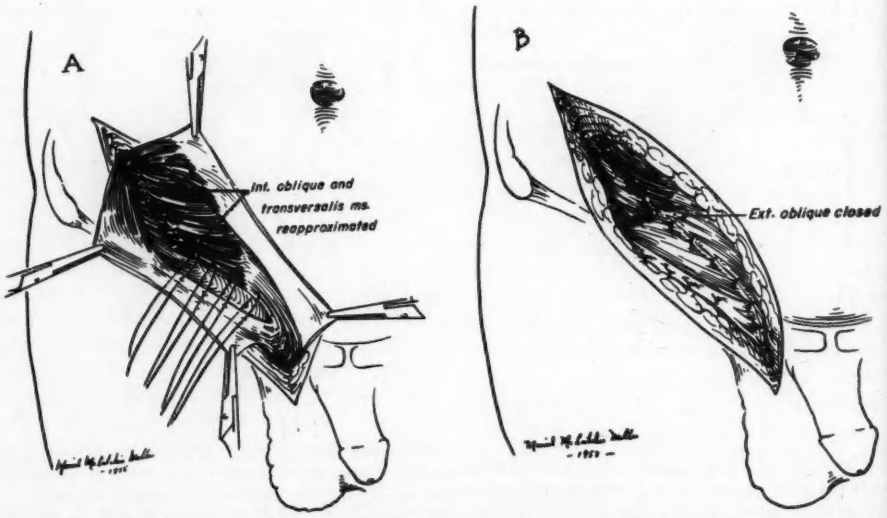

FIG. 5. *A*, wound closure. Peritoneum has been closed and internal oblique and transversalis muscles reapproximated. Edge of internal oblique and conjoined tendon being approximated to inguinal ligament to obliterate inguinal canal. *B*, external oblique muscle and fascia have been reapproximated. Subcutaneous tissue and skin will now be closed.

tion of the aorta and the common iliac arteries are carefully palpated for nodes or a metastatic mass. If a mass is felt, it is very carefully palpated to determine whether it is probably removable or not. Careful note is made as to the position of palpable nodes, and as to whether they may be bilateral. In closing the wound, first the peritoneum is closed, and then the oblique and transversalis muscles above the internal ring are carefully re-approximated with interrupted mattress sutures (fig. 5, *A*). Then the inguinal canal is closed as in a Bassini herniorrhaphy, suturing the internal oblique and the conjoined tendon to the inguinal ligament to obliterate the internal inguinal ring and the inguinal canal. Finally the external oblique muscle and fascia are closed (fig. *5*, *B*).

In the few cases in which we have done this, the wounds have healed well, and the patient's hospital course has not thereby been unduly prolonged or complicated. In our opinion, the slight extra risk and morbidity of performing this operation in conjunction with high orchiectomy are more than compensated for by the value of the information secured thereby. This information has allowed for more intelligent planning of the patient's subsequent treatment, be it retroperitoneal node dissection or x-ray therapy. Also, by discovering unsuspected extensive inoperable metastases, it has been made possible for some patients to avoid major retroperitoneal explorations which were doomed to failure in advance. Moreover, if a retroperitoneal node dissection is performed later, the high dissection and ligation of the internal spermatic vessels and lymphatics definitely simplify the second procedure.

SUMMARY

Ninety-six and one-half per cent of all testicular tumors are of germinal cell origin, containing totipotent cells capable of giving rise to any tissue of the body. Thus they are basically mixed tumors and their classification into separate types has been difficult.

As an exception, "pure" seminomas do occur. These are very radiosensitive, and x-ray therapy is the treatment of choice, giving a high rate of cure.

True chorioepitheliomas metastasize rapidly and widely by the bloodstream, are very radioresistant and are almost always fatal. No known treatment is effective.

Between these two extremes are the teratomas, teratocarcinomas and embryonal carcinomas—mixed tumors which have both radiosensitive and radioresistant components. This group comprises 60 per cent of testicular tumors.

Except for the chorioepitheliomas, the usual metastases of testicular tumors are lymphatic, following the course of the internal spermatic vessels to lymph nodes located in the area where these vessels join the aorta, inferior vena cava and left renal vein. Thus it is in this preaortic and precaval region of the renal pedicles and just below that the primary lymphatic metastases from testicular tumors occur.

The aim of radical orchiectomy and retroperitoneal lymph node dissection (introduced by Hinman) is to remove the tumor together with its primary lymphatic metastases before the disease has spread beyond this zone.

The combination of such surgery for the extirpation of radioresistant metastases together with x-ray therapy to take care of radiosensitive elements and any stragglers which have escaped surgical removal seems most likely to be effective—and this is our program of treatment.

From January 1949 through June 1957, 26 patients at the Veterans Administration Hospital in Boston had 32 explorations (6 bilateral) for retroperitoneal lymph node removal.

Seven patients had disease which was inoperable and died within a few months.

Eight patients had no malignancy found in the nodes removed, but despite this two died of malignancy. The other six are living and well for an average of 4⅓ years.

Eleven patients had proven metastases removed by surgery followed by x-ray therapy. Four of these died of their disease, but seven (64 per cent) are living and apparently free of disease for varying periods of time, averaging 6 years per patient, since operation and x-ray therapy.

Our figure of 64 per cent compares favorably with a similar but larger group in which another author reported only 46 per cent living for at least 5 years. Our more favorable survival figures may well be ascribed to our routine use of the thoracoabdominal incision which gives definitely better exposure of the region of the kidney pedicle than the flank incision used in the other group. The superiority of the thoracoabdominal incision was demonstrated to us by three pa-

tients in each of whom we removed metastases not reached by a previous recent flank incision. Two of these patients are "cured" for 9 years and 6 years respectively—the other died of his disease after 2½ years.

There were no postoperative or post-irradiation deaths. Complications were one case of mild lower nephron nephrosis, and three cases of moderate hemothorax requiring thoracentesis by needle. Also, unexpected nephrectomy was performed twice—once in an effort to remove tumor involving the renal pedicle and once on account of accidental trauma to the renal artery during the dissection.

It is our opinion, and that of several others, that, in the embryonal carcinoma-teratoma-teratocarcinoma group, retroperitoneal node dissection in addition to x-ray therapy has given better results than x-ray therapy alone.

Since abdominal examination and x-rays failed to reveal the presence of gross retroperitoneal metastases in more than half of the cases where they existed, we have been performing a limited abdominal exploration at the time of the initial orchiectomy through an upward prolongation of the orchiectomy incision. This has not added any undue additional risk or morbidity, and has given information as to the absence, presence, or extent of retroperitoneal metastases which has been very valuable in planning the subsequent treatment of the case. If inoperable metastases are found the patient is not subjected to thoracoabdominal retroperitoneal exploration, and deep x-ray therapy can be started without delay in establishing the diagnosis.

This operative procedure is described with drawings.

ADDENDUM

Since our paper was presented, Dr. Willard E. Goodwin has called our attention to an abstracter's comment by him (Urol. Survey, **6:** 447, Dec. 1956) previously unknown to us. In this he refers to Dr. Silver's and his procedure of performing a limited abdominal exploration at the time of the initial orchiectomy. While the description of this procedure is not given in detail, it may well be similar to ours, and the principle of exploration at the time of orchiectomy is the same.

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DISCUSSION

DR. W. HOUSTON TOULSON (Baltimore, Md.): These have been two very unusual papers and very authoritative in my estimation. It is seldom that a group hears great papers like these two.

I particularly want to discuss one phase of Dr. Mallis's paper having to do with seminoma in which the patient, to me, had quite an interesting condition.

Of course, we know from these statistical data which were shown on the screen that seminoma, of all tumors, is the most benign. The patient whom I wish to discuss briefly is a chap who came to our clinic in 1941 with what we diagnosed as a seminoma of the right testis. After he had a simple removal of the testis, followed by radiation therapy, his progress was satisfactory until 1947, when he came in with a similar situation in the opposite testis. This too was not of any rarity, but it was of sufficient interest to discuss it today.

After simple removal of the second tumor, it was followed by deep x-ray therapy. It so happens that this chap is an intelligent lawyer, very cooperative, and is naturally tremendously interested in his welfare and in the outcome. He comes regularly for checkups and practically any investigative work we might want to do.

He volunteered, after 18 years of known testicular tumor, that in spite of the loss of both testes he has erections, that he has intercourse, that he even has a mild, slight ejaculation.

One now gets into the conjectural field as to what group of androgenic cells has taken over this function Presumably it is the adrenals or hypophysis.

DR. JOHN A. TAYLOR (New York, N. Y.): I want to discuss a few cases that I had before the Army went into business.

I was very much impressed with this series of cases and with the wonderful results, and very much interested in bilateral lymphadenectomy, because Ben Barringer, years ago, said that 70 per cent of the autopsy material he examined showed bilateral involvement.

The first patient was 29 years old in 1932. He had a teratoma, positive A-Z tests. This was removed, followed by x-ray. In 1944 he returned with a seminoma, with abdominal metastasis the size of a grapefruit. I showed these cases here in 1945. He had caudad displacement of the transverse colon and displacement of the ureter. With radiation it disappeared.

This patient is a golf and tennis instructor at present and is enjoying good health 26 years after his first operation and 14 years after his second.

The second case was a 26-year-old patient, in 1927. He had a right seminoma. He had a left seminoma in April 1932. I wrote to him. He is a Washington correspondent. I have his letter here. He says his general health is good. He suffers "from mild but unpleasant mental depressions, from which a lot of magazine writers seem to suffer also." This letter is dated October 23, 1957, thirty-one years after his first operation and 26 years after the second.

The third patient was a man of 23 in 1937, who had a positive Friedman test, a growth in the testicle with clinical evidence of gynecomastia and very severe acne. The growth was removed with a high inguinal ligation, followed by radiation therapy. I wrote to him, and in his letter of October 1957 he says he is well. He has three boys aged 13, 11½ and 10, which I mention only because radiation is hazardous to the other testicle.

He said, "We both have given up smoking, and my weight is at the dangerous point of 165 pounds."

That is a case of chorionepithelioma 21 years after it was removed. I have had some people question it. At that time, Dr. Francis Carter Wood, who with Dr. Ewing was one of the experts on carcinoma, made the microphotographs for me. I think I will go along with his diagnosis.

DR. REED M. NESBIT (Ann Arbor, Mich.): I want to comment on the matter of irradiation in teratocarcinomas. We have all been led to believe that these are highly resistant to irradiation, and sometimes we wonder whether it has any value at all in that group.

One of the Walter Reed cases came to my attention within the last year, that of a man who lives in the nearby city of Jackson, Michigan, who had a teratocarcinoma that was treated, as you have heard described, at Walter Reed Hospital. Following this operation he had ex-

tensive irradiation. He too has sired two sons since this extensive irradiation.

After about five years a pulsating tumor developed in his frontal bone of the skull and he went back to Walter Reed for irradiation therapy in that area. When I saw him his only complaint was that he had alopecia in the area that was treated, but no evidence of recurrent tumor. He was not operated on in that area, and apparently the secondary tumor disappeared entirely. He is a 10- or 15-year survival now. He had a teratocarcinoma which apparently was very responsive to irradiation.

Dr. Vincent J. O'Conor, Sr. (Chicago, Ill.): There are many imponderables about patients who have testicular tumors. One patient seen recently had a high left orchiectomy for a teratocarcinoma with no dissection of the renal pedicle. None of the nodes were positive. This was followed by deep x-ray therapy. Four and a half years later he appeared with gross hematuria and we found that he had a papillary carcinoma of the right renal pelvis with no evidence of involvement of the ureter or bladder. Nephroureterectomy was done on the right side, and at the time of this procedure a moderately enlarged node was found lying alongside the inferior vena cava. This was about 1½ cm. in diameter and was removed. I could find no other nodes on the right side of the large vessels. I did not explore the left side since node dissection had previously been done. The microscopic examination of this node showed marked fibrosis, but in the center was some apparently viable carcinoma tissue. This patient has been followed now for almost five years and no evidence of recurrence has been noted. It is conceivable that recurrence will appear even though the carcinoma seemed to be trapped in the center of the lymph node.

Another patient, upon whom I carried out orchiectomy 14 years previously, appeared in New York and consulted Dr. Victor F. Marshall. This had been a teratocarcinoma. He had had a simple high orchiectomy followed by x-ray. Dr. Marshall found that there was recurrence of the teratocarcinoma in the same inguinal region. This was 14 years after operation. The patient has now been relieved of this recurrence for a period of about five years, and has shown no further recurrence up to this date.

Dr. Hugh J. Jewett (Baltimore, Md.): I should like to ask Dr. Patton and Dr. Chute if they have had any success with the use of progesterone or any other chemicals in cases of chorionepithelioma of the testis.

Dr. Frank Hinman, Jr. (San Francisco, Cal.): I have a few considerations I would like to bring before you.

First, the problem of only 2000 roentgens for seminoma: If all seminomas metastasized as pure seminomas, this would be adequate; but the fact that the initial tumor appears homogeneous at the time of operation is no guarantee that it occasionally won't metastasize as a more differentiated type and more radioresistant type. So, it is our custom to give these patients 3600 to 3800 R.

Second, Dr. Chute abhors biopsy at the time of orchiectomy. I would agree with him because of the danger of spread. However, there is a halfway point. Occasionally we see patients who are operated on for carcinoma of the testis after a delay because it was impossible to differentiate tumor from epididymitis or other more benign lesion.

The midway point (I am sure some of you are doing this, and it certainly isn't original with us) is a tourniquet around the cord, after exposure through the inguinal canal, so that the blood supply is cut off, then exposing the testis. One does not need to biopsy it once it is out in the hand. It is very easy to tell whether or not it is a neoplasm, and one has not spread it.

We too have been exploring through the inguinal incision for inoperable nodes. I know Dr. Willard E. Goodwin has been doing this for some time also. It is very useful, since it often saves a large incision later.

Finally, I would like to suggest using the aortectomy incision, which general surgeons use when removing aortas, for node dissections. You will find it is much easier than through the chest or through the flank: a long midline incision alongside the zyphoid clear to the symphysis, going transperitoneally, mobilizing the cecum, running an incision up the posterior peritoneum in the midline and lateral to the cecum. Then the whole cecum and the whole small intestine can be lifted out of the abdomen, and put into a plastic turkey bag. Then the operation can proceed, beginning well above the renal pedicles on both sides, with equal exposure on either side.

On the left side, of course, one has to either

sacrifice the inferior mesenteric vessels or pass the tissue resected underneath them and underneath the descending colon. This, however, allows a complete node dissection in less operating time than the other incisions.

PRESIDENT GEORGE F. CAHILL (New York, N. Y.): I personally have had a great deal of pleasure listening to these two papers today, because about twenty-seven years ago I read a paper on 40 cases of radical removal of the testis, and in this organization only two men agreed with me at that time. One was Frank Hinman, Sr., and the other was Hugh Young. It is a great pleasure to note what has happened in those 27 years.

DR. JOHN F. PATTON (Washington, D. C.): I wish to thank the discussants for their remarks. I take no credit for this series because I was not at Walter Reed during the period this report covers. There were various individuals involved in directing the treatment of these patients and in formulating the policies. Chief among these were Lewis and Kimbrough in the early period and later Schwartz and Van Buskirk.

We have made no attempt to compare the over-all data with previous reports based on a part of this series, nor with reports from other clinics. Also, it does not seem practical to compare the two groups treated by irradiation and by lymphadenectomy. In order to draw any valid conclusions it would be necessary to know how many patients in each series had involvement of the retroperitoneal nodes at the time treatment was instituted. We have that information in those treated by lymphadenectomy but not in those treated by irradiation. Even if one were to open the retroperitoneal space for inspection or to take a biopsy prior to irradiation therapy, this information might not be obtained because in doing a lymphadenectomy one may find only two or three positive nodes in a total of thirty or thirty-five removed.

In reply to Dr. Nesbit, I believe the patient he refers to had a lesion in the skull which was suggestive of metastasis but it was not proven by biopsy.

Dr. Jewett asked about the use of chemical compounds. We have used nitrogen mustard in combination with ACTH but the results have been disappointing. Dr. Lipsett and his coworkers at the National Cancer Institute are doing considerable work with chemical compounds, one of which is amethopterin. We have contributed some patients for consideration of this therapy but that is as far as we have gone to date.

I would like to say a word about the transperitoneal approach in lymphadenectomy, which Dr. Hinman mentioned. We have been using it during the past year and like it very much. In fact, we are showing a motion picture of the technique at the coming meeting of the American Urological Association in New Orleans. We believe that the lymphadenectomy should be bilateral in all cases, and the transperitoneal approach certainly gives more adequate exposure, particularly in the critical area around the renal pedicle.

DR. RICHARD CHUTE (Brookline, Mass.): I wish to thank the discussers for their interesting discussion.

To speak of Dr. Nesbit's remarks, I would agree with him that not all teratomas are radioresistant, and some of them seem to be quite radiosensitive. I think it is a terribly important thing for all general surgeons to know that a pulsating, hot tumor, be it in the sternum as reported by George Crile, Jr., in the skull or in the ilium, is usually a metastasis which has about an equal chance of having originated in a hypernephroma or in a carcinoma of the thyroid.

Dr. Nesbit, if we do retroperitoneal node dissection following this preliminary exploration, we bring the incision down, as I endeavored to show in the last slide, so that it just about meets the lower incision. We have been using recently a thoracoabdominal incision in the tenth rib interspace, but I think from the remarks of Dr. Hinman and Dr. Patton we may well be changing our tune and trying that.

Dr. O'Conor brought up a very important point, which is that very rarely these tumors may recur after many years of quiescence. In view of this, while I agree with Dr. Patton that five years is usually long enough to allow for the appearance of any recurrence which is going to take place, I still think you have to follow these cases indefinitely and that you can't consider them really cured for at least fifteen to twenty years.

We have not used progesterone at all.

I would not expect any discussion on testicular tumors to take place when there was a Hinman in the audience, and not have him speak right up, and I am glad Frank did. As Dr. Ewing said

years ago, it is important to remember all the time that all these tumors are basically mixed. We may have pure chorionepithelioma or what we consider pure seminoma, but there is very apt to be just a little something else mixed in, and of course, some of them are exceedingly mixed.

I would go along with him in giving lots of irradiation, although as you all know, in the early cases at Walter Reed, as reported by Lloyd Lewis, a number of deaths were due to irradiation nephritis.

As for this biopsy business, we have frequently put a rubber-shod clamp on the cord before we actually clamp and cut the cord. By "biopsy" I mean actually cutting into the tumor on the table. I suppose in a special instance you could have the tumor isolated on a special drape, and you could biopsy it and then change your gown, gloves, instruments and drapes after the biopsy, and isolate the tumor carefully, but as a rule I think biopsy is to be absolutely condemned. However, inspection with a tourniquet type of clamp on the cord, I think, is very reasonable. I am glad to hear that Dr. Willard E. Goodwin has been doing this.

I am delighted to hear about this aortic graft incision. I have been looking at this a little bit from the point of view of transplants of the renal artery, but I frankly hadn't thought of it in this connection.

I wish to thank my discussers very much.

PRESIDENT CAHILL: I would like to bring up one point that both authors should answer. In the Guiteras Lecture a number of years ago a speaker talked on testicular tumors. I was sitting in the front row and I heard him say (although it never appeared in his published paper) that it was too bad the radical operation for removal of testicular tumor had such a high mortality that it wasn't done universally.

I want to call attention to the fact that there is a very low mortality in these radical operations; is that correct?

DR. PATTON: We have had one death in 52[illegible] cases.

PRESIDENT CAHILL: The mortality isn't even thought about any more.

We thank you two gentlemen for your splendid papers.

EXPERIMENTAL STUDIES IN ACUTE RETROPERITONEAL CARBON DIOXIDE INSUFFLATION

B. MARVIN HARVARD, ROBERT R. WHITE AND JAMES F. WALSH, III

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Gas has been used as a contrast medium for the radiological visualization of various parts of the human body since the injection of air into the cerebral ventricles by Dandy[1] in 1918. Cahill[2] described a technique for translumbar perirenal air injections in 1935 for demonstration of the kidneys and adrenals, but it was not until the work of Rivas,[3] utilizing the presacral approach, that the use of perirenal pneumography became widespread.

Minor complications involving the technique include abdominal and flank pain; emphysema of the scrotum, mediastinum, and neck; pneumothorax; and inflammatory reaction at the site of injection. The major complication is gas embolism. In a recent nationwide survey conducted by Ransom, Landes, and McLelland,[4] a total of 9,201 cases done by the presacral route using air, oxygen, helium, and carbon dioxide were collected. They reported 58 deaths (0.26 per cent) and 64 nonfatal reactions resulting from gas emboli. The apparent safety of carbon dioxide has been demonstrated by its use intravenously for the purpose of obtaining roentgenograms of the cardiac chambers.[5] Its application to presacral pneumography has been limited, however, due to its rapid absorption rate which results in radiographs of poor diagnostic quality. A modification of the technique has been described by Landes and Ransom.[6] They injected larger volumes of carbon dioxide and obtained adequate perirenal and suprarenal accumulations of gas. It is apparent that a large amount of gas must be introduced over a short period of time in order to produce satisfactory results.

We have been investigating the side effects and complications produced by injecting carbon dioxide by the presacral route in amounts far in excess of the volumes necessary to produce satisfactory diagnostic radiograms. Further study has been directed toward the tolerance of large amounts of gas received intravenously.

METHODS

The test animals were mongrel dogs of 12 to 23 kilograms, anesthetized with intravenous nembutal. Following the technique described by Landes and Ransom,[6] a Vim-Silverman needle was introduced into the presacral space on both sides of the midline, and polyethylene tubing was inserted via the needle and taped in place. Carbon dioxide gas was then introduced in volumes from 10,300 cc to 20,400 cc (872 cc per kilogram to 1000 cc per kilogram) at approximately 200 cc per minute. Serial films were taken at three-minute intervals. All animals were in the prone position and were maintained in this position during the injection of the gas. Several animals were given carbon dioxide intravenously at rates between 100–300 cc per minute via an antecubital vein. Serial electrocardiograms were made on these animals during and after injections of the gas.

RESULTS

In all instances prompt visualization of the retroperitoneal organs was uniformly noted following injection of the first 1200 cc gas (fig. 1). Additional gas did not add or detract from the diagnostic quality of the x-ray, but did produce some other interesting gross and radiologic changes. Massive subcutaneous emphysema was produced, extending from the hind-limb to the mandible, producing an increase in anteroposterior diameter of 10 cm. at the level of the xiphoid process in one instance (fig. 2). Comparable

[1] Dandy, W. E.: Ventriculography following the injection of air into cerebral ventricles. Ann. Surg., **68:** 5, 1918.

[2] Cahill, G. F.: Air injection to demonstrate adrenals by x-ray. J. Urol., **34:** 238, 1935.

[3] Rivas, M. R.: Roentgenological diagnosis, generalized subserous emphysema through a single puncture. Am. J. Roentgen., **64:** 723, 1950.

[4] Ransom, C. L., Landes, R. R. and McLelland, R.: Air embolism following retroperitoneal pneumography: a nationwide survey. J. Urol., **76:** 664, 1956.

[5] Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H. III, Lynch, P. R. and Barrera, F.: In vivo visualization of intracardiac structures with gaseous carbon dioxide. Am. J. Physiol., **186:** 325, 1956.

[6] Landes, R. R. and Ransom, C. L.: Technique for the use of carbon dioxide in presacral retroperitoneal pneumography. Surg., Gynec. & Obst., **105:** 268, 1957.

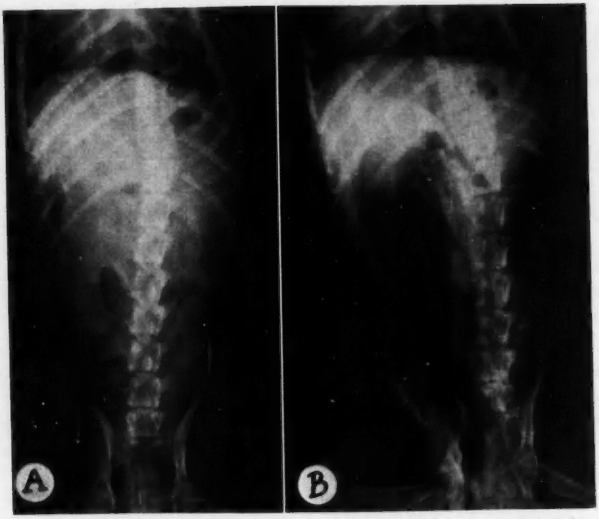

FIG. 1. *A*, control. *B*, visualization of retroperitoneal organs following injection of 1200 cc carbon dioxide.

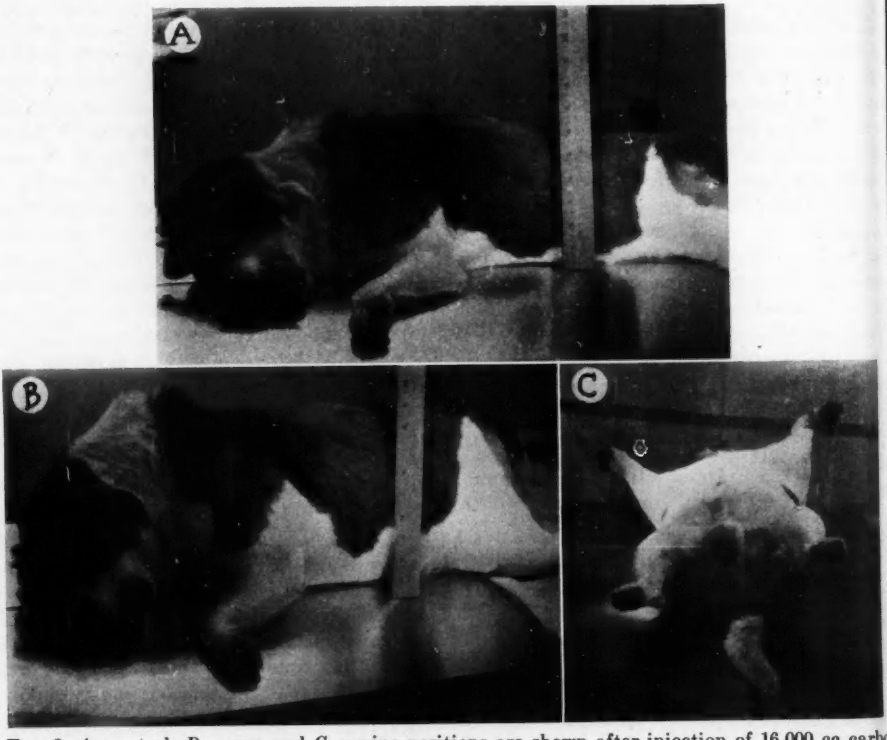

FIG. 2. *A*, control. *B*, prone and *C*, supine positions are shown after injection of 16,000 cc carbon dioxide in retroperitoneal space.

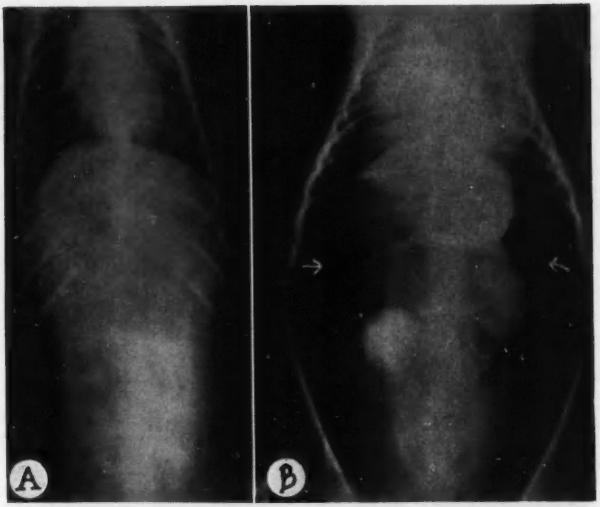

FIG. 3. *A*, control. *B*, parietal peritoneum is being pressed medially together with intraperitoneal organs by dissecting gas.

distention was noted in all test animals. Parietal peritoneum was easily seen to be dissected free of the dorsolateral abdominal wall (fig. 3). Additional findings included pneumoperitoneum, several instances of partial pneumothorax, and one complete left pneumothorax (fig. 4). Marked respiratory stridor was noted in one animal. This we believed was due to tracheal compression from subcutaneous emphysema of the neck. Although respirations were labored in each animal, hyperpnea was not observed except with the occurrence of complete unilateral pneumothorax. Respiratory rate in this instance returned to the control level 20 minutes after the total amount had been injected, and was coincident with resolution of the pneumothorax. All animals survived and were observed to remain well for at least one week following injection. Autopsy of one animal sacrificed immediately after receiving a total of 16,000 cc (1000 cc per kilogram) of carbon dioxide by the presacral route revealed pneumoperitoneum and partial atelectasis of the right lung (fig. 5). There was no demonstrable intravascular gas. Sections taken from other organs including heart, small and large bowel, adrenals, kidneys, bladder, pancreas, liver and muscle revealed no microscopic abnormalities.

Our experience with intravenous carbon dioxide gas indicates that the tolerance of the intravenous gas is roughly proportional to the rate at

FIG. 4. Complete left pneumothorax after injection of 10,300 cc carbon dioxide (873 cc/kg.). Note also partial right pneumothorax.

which it is injected. Ten thousand cubic centimeters of carbon dioxide were given intravenously to one animal at a rate of 100 cc/min. (8.4 cc/min./kg.) without demonstrable adverse effect. When given at 200 cc/min., relatively large amounts (30.4 cc/min./kg.) were tolerated before apnea occurred, and over double this amount

(65.2 cc/min./kg.) was required to produce cardiac arrest. In each animal hyperpnea developed during injection of the gas. When individual tolerance levels were reached, hyperpnea ended abruptly in apnea. Injections at the rate of 300 cc/min. produced rapid onset of respiratory arrest, bradycardia, and cardiac arrest unresponsive to the usual resuscitative measures. Electrocardiogram changes during apnea are nonspecific and transitory. These changes include

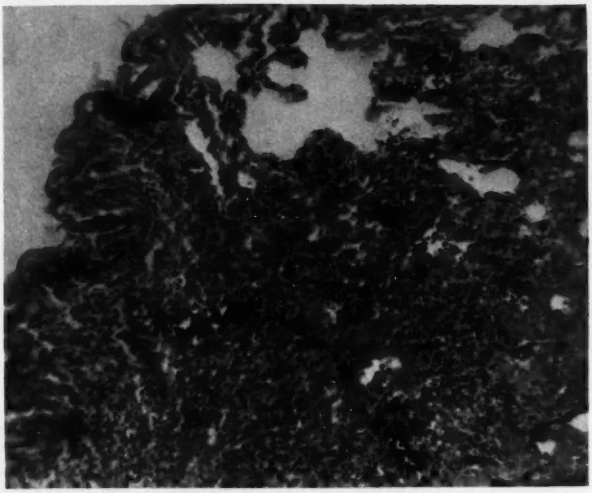

FIG. 5. Lung (× 360). Note atelectasis and congestion of alveolar arterioles

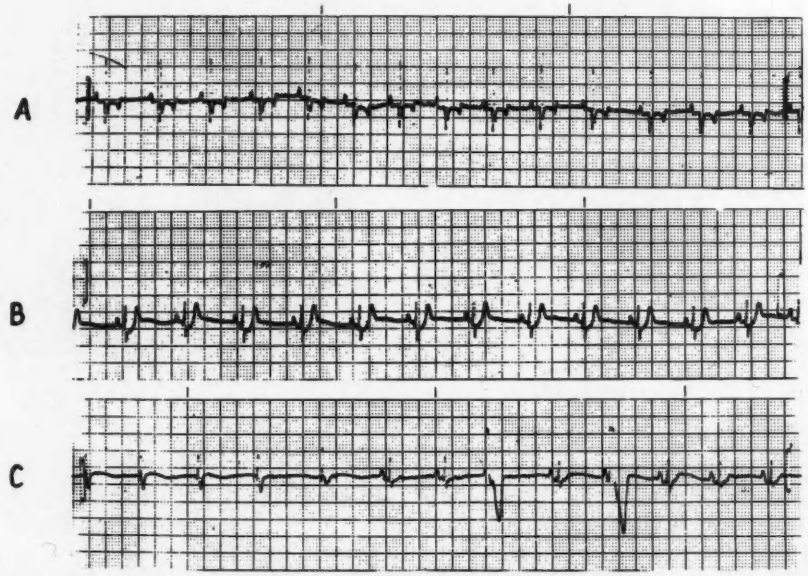

FIG. 6. *A*, lead II. *B*, decrease in amplitude of QRS complex, abnormal deviation of S-T segment inversion of T wave. *C*, nodal rhythm and extrasystoles.

decrease in amplitude of the QRS complex, abnormal deviations of the S-T segment, and inversion of the T-wave. Larger quantities of gas produce extrasystoles and nodal rhythm before arrest occurs (fig. 6).

DISCUSSION

The wide margin of safety from embolic phenomena in the use of carbon dioxide in the retroperitoneal space is readily evident. The disadvantages encountered are primarily technical and as such offer no contraindications to its use. The rapid solubility of carbon dioxide requires that relatively large volumes of gas be introduced over short periods of time. Complications secondary to gas embolism seem to be nearly impossible to produce. Moore and Braselton,[7] injecting carbon dioxide into the pulmonary vein of dogs, observed bubbles of gas to enter the coronary arteries and to disappear into solution without producing any ill effect. In our experience there has been a similar rapid absorption of the gas when injected intravenously. Hyperpnea occurred in all animals during intravenous injection, but only occurred during retroperitoneal injection when pneumothorax developed.

Detailed studies of cardiovascular-respiratory effects of intravenous carbon dioxide have been made by Oppenheimer and associates.[5] Systemic hypotension and abnormal electrocardiograms were noted by them to exist for the length of time corresponding to the presence of gas in the cardiac chambers, but these effects were transitory and produced no untoward effects.

Thus, there seems to be a wide margin of safety in the use of carbon dioxide in the retroperitoneal space. Efforts to kill the animals in this series by presacral carbon dioxide injection were unsuccessful, and all animals survived. Volumes far in excess of those necessary for radiographs of good diagnostic quality produced only transitory complications. In this preliminary report of a current investigation, we hope to reinforce the use of retroperitoneal pneumography as a safe and dependable diagnostic tool.

SUMMARY

A series of animals were subjected to massive retroperitoneal carbon dioxide injections and the effects noted radiographically. No irreversible complications secondary to retroperitoneal gas insufflation were observed. All animals survived. Observations with intravenous injection of carbon dioxide indicated the animal's tolerance to be roughly proportional to the rate of injection.

We wish to thank Dr. Alan Skorneck, chief of the Department of Radiology of the West Haven Veterans Hospital and Dr. Massimo Calabresi of the Department of Cardiology, for lending the use of their facilities, and for their advice and assistance.

[7] Moore, R. M. and Braselton, C. W., Jr.: Injection of air and of carbon dioxide into the pulmonary vein. Ann. Surg., **112:** 212, 1940.

DISCUSSION

DR. FRANK COLEMAN HAMM (Brooklyn, N. Y.): I am very much interested in this experimental work on retroperitoneal insufflation. Just before coming here we had started an analysis of our experience with injection of gas into patients and we have done this in over 700 patients.

In our earlier studies we injected air. It is the least desirable gas to use as it is composed principally of nitrogen, which of course is insoluble.

On the other hand, out of the 700 patients we had no fatality and no really serious complications.

Next we experimented with oxygen, which is a little more soluble than nitrogen; and generally speaking, the results were pretty good. However, I believe the safety of the procedures lies in limiting strictly the amount injected. Originally we injected about 1,500 cc. More recently we have used only 350 to 500 cc on either side. I think this point is extremely important.

In the last year we have experimented with carbon dioxide because it is the most widely used gas and certainly the most soluble. The gynecologists have used it for years for tubal pregnancy tests, and they have shown in these tests that the gas bubbles right up the iliac and one can see it in the roentgenogram.

However, we have not had good results in visualizing the retroperitoneal structures because carbon dioxide is absorbed too rapidly, at least in the amounts we give.

I have enjoyed this paper very much. Perhaps we will have to revise the amount we are injecting, but so far oxygen has given us the best results.

STUDIES OF HORMONAL CHANGES IN RELATION TO CANCER OF THE PROSTATE: A PROGRESS REPORT

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From the Department of Surgery, Peter Bent Brigham Hospital, Harvard Medical School and the Biologic Research Laboratory, Harvard School of Dental Medicine, Boston, Mass.

The response of prostatic cancer to antiandrogenic therapy is probably the most outstanding phenomenon in the study of cancer. Although it is commonly recognized that hormonal therapy such as castration, estrogen administration or adrenalectomy tends to alter the natural course of this disease, the over-all hormonal environment in which the disease arises and the complex changes which occur in the environment after therapy are only partly understood.

This report is a résumé of a long range study instituted in 1953 which is presently being continued in our laboratories directed toward a more complete understanding of hormonal changes associated with the treatment of prostatic cancer. Some of this material has been previously reported,[1-4] however, for clarity and cohesion the studies are presented in their natural sequence. The systematic approach to this problem has resulted in the study of androgen excretion in selected groups of patients. First, urinary androgen was determined in young and old men, the latter group divided into those with and without prostatic cancer. Next, the effect of orchiectomy was studied. Adrenocorticotrophic hormone (ACTH) was administered to young and old intact men and again following orchiectomy in the latter. Androgen excretion was then determined after bilateral total adrenalectomy. Most recently we have completed studies of androgen excretion in patients receiving estrogen before and after orchiectomy.

Supported in part by Research Grants CY-2051(C-3)(Endo) and C-2056, National Cancer Institute, National Institute of Health, United States Public Health Service, and American Cancer Society Grant No. t-IR-44H2.

[1] Harrison, J. H., Leman, C. B., Munson, P. L. and Laidlaw, J. C.: Androgen, gonadotrophin and steroid excretion in man before and after adrenalectomy. Tr. Am. Assoc. Genito-Urin. Surg., **46:** 84-88, 1954.

[2] Harrison, J. H., Leman, C. B., Munson, P. L. and Laidlaw, J. C.: Hormone excretion before and after castration and adrenalectomy. New Eng. J. Med., **252:** 425-428, 1955.

[3] MacFarlane, D. A., Leman, C. B., Munson, P. L. and Harrison, J. H.: The effect of ACTH administration on the urinary excretion of androgens and other steroids by old men in comparison with young men: Preliminary report. Tr. Am. Assoc. Genito-Urin. Surg., **47:** 51-54, 1955.

[4] Munson, P. L., Goetz, F. C., Laidlaw, J. C., Harrison, J. H. and Thorn, G. W.: Effect of adrenocortical steroids on androgen excretion by adrenalectomized orchiectomized man. J. Clin. Endocrinol., **14:** 495-508, 1954.

MATERIAL AND METHODS

Subjects in this study were patients under care and personnel at the Peter Bent Brigham Hospital during the past five years. Histologic confirmation was obtained in all patients with prostatic carcinoma and the age range at the time of diagnosis was 52 to 82 years. Determinations were performed on aliquots of refrigerated 24-hour urine specimens. Although studies have included the colorimetric estimation of urinary 17-ketosteroids[5] and 17-hydroxycorticoids,[6] the bulk of this report is based on the biologic assay of androgenic activity using the chick comb technique.[7] This consists of quantitation of the response of the comb weight of the immature chick to direct application of urinary extract by comparison with responses of chicks treated with standard androsterone solution and comparison with control chicks.[8] The method is most tedious and involves the use of 100 to 200 birds for each analysis; nevertheless, it is a most sensitive test, determining as little as 0.05 mg. of androsterone. By this method the quantitative assay of as little as 0.25 international units (i.u.) of androgen is

[5] Klendshoj, N., Geldstein, M. and Sprague, A.: Determination of 17-ketosteroids in urine. J. Clin. Endocrinol., **13:** 922, 1953.

[6] Reddy, W. J., Jenkins, D. and Thorn, G. W.: Estimation of 17-hydroxycorticoids in urine. Metabolism, **1:** 511, 1952.

[7] Rakoff, A. E., Paschkis, K. E. and Cantarow, A.: Androgen assay on 3-day old male chicks. Proc. Soc. Exper. Biol. & Med., **55:** 124, 1944.

[8] Zarrow, M. X., Munson, P. L. and Salter, W. T.: A comparison of androgens determined biologically and 17-ketosteroids determined chemically in urine (normal and abnormal). J. Clin. Endocrinol. & Metab., **12:** 971, 1952.

possible; an amount less than 1/200 the daily excretion of a normal young man.

DISCUSSION OF RESULTS

1) *Studies of intact young and older men.* The initial studies of 17-ketosteroids and androgen measured biologically in young and old men show a definite decrease with advancing age.[2] In 11 young men aged 19 to 32 the androgen excretion in 24 hours varied from 30 i.u. to more than 90 i.u. with a mean of 62 i.u. Nine older men ranging in age from 50 to 84 years showed excretion ranging from 5 i.u. to a maximum of 30 i.u. Sixteen patients with cancer of the prostate showed a similar variation ranging from 7 to 35 i.u. No variation in 17-ketosteroid or 17-hydroxycorticoid levels was noted between these last two groups except in markedly debilitated patients.

From these studies we note that there is no essential abnormality of androgen production in the patient in whom carcinoma of the prostate develops other than the diminution common to the older age group. In fact, we find that carcinoma becomes apparent in an environment of diminished androgen production. As Huggins pointed out some years ago with reference to benign prostatic hyperplasia, it is probable that prostatic tissue in the elderly is more sensitive to much smaller changes in the amount of circulating hormone.[9] It has been found that a further reduction in the already spontaneously diminished androgen levels of the aged has a profound effect on the growth of prostatic carcinoma. Consequently, orchiectomy usually produces dramatic clinical improvement even in patients with extremely low androgen titers.

2) *The measured effect of castration.* Studies of androgen excretion before and after orchiectomy in 12 patients with carcinoma of the prostate show a decrease in androgen in every case. In one patient there was a transient rise noted on the first postoperative day, probably related to adrenal stimulation from the stress of surgery. A subsequent determination showed the expected fall. In 6 cases the decrease of androgens was approximately 33 per cent.[2]

These findings are of interest in light of present concepts of androgen production, namely, that approximately one-third of androgen arises from the testis and two-thirds from the adrenal cortex. Studies of total 17-ketosteroid excretion have not borne this out, and, in general, have been rather inconclusive. Yet by determining the biologically active androgenic metabolites we find a fairly consistent 33 per cent fall after orchiectomy. The discrepancy between the results of 17-ketosteroid levels and androgens measured biologically is explained by recent fractionation methods which demonstrate that the most active biologic component, androsterone, represents only a small fraction of the measured total 17-ketosteroids.[10] Androsterone constitutes approximately 25 per cent of the total 17-ketosteroids in the intact male and in the castrate 15 per cent of the latter.

3) *The effect of ACTH on androgen excretion.* The effect of ACTH on urinary excretion of androgen was studied in young men, elderly men and in orchiectomized patients with prostatic cancer.[3] In 10 young men given 25 units of ACTH intravenously there was a rise of 5 to 80 i.u. per 24 hours in every case but one; however, repetition in this man produced a similar increase. The mean increment in this group was 30 i.u. In 11 older men there was a similar response ranging from 6 to 60 i.u. with a mean increment of 20 i.u. Although the absolute increment is less with ACTH stimulation in this older group, the relative percentile increase in the older man is greater than in the young. This suggests that adrenal androgen production plays a relatively more important role in the older patient. In elderly orchiectomized men there was an increment of 7 to 60 i.u. with a mean of 21 i.u.; quite similar to the response in the elderly intact men.

The similarity of androgen excretion in these last two groups bears out several basic concepts of endocrinology: First, the effect of ACTH is purely on the adrenal cortex, the androgen production of the testis probably being under the control of pituitary gonadotrophin (interstitial-cell stimulating hormone, ICSH, or, synonymously, luteinizing hormone, LH). Second, as shown by the response of the orchiectomized group, androgen production, presumably from the adrenal cortex, *is* stimulated by ACTH. This response to ACTH by the orchiectomized patient may be considered similar to that anticipated in the every day response to stress encountered by these patients.

[9] Huggins, C.: The etiology of benign prostatic hypertrophy. Bull. New York Acad. Med., **23:** 696, 1947.

[10] Birke, G., Franksson, C. and Plantin, L. O.: On the excretion of androgens in carcinoma of the prostate. Acta Endocrinol., **15:** Suppl. 17, 1, 1954.

This further demonstrates the mechanism by which continued androgen stimulation of prostatic cancer may be present even after orchiectomy. Hence, removal or suppression of the adrenal source is a logical step toward reducing androgen stimulation.

4) *The effects of adrenalectomy and cortisone administration.* As anticipated, androgen excretion is markedly diminished by adrenalectomy.[11] Following adrenalectomy, however, measurable biologic activity persists even when corticoid replacement has been withheld for as long as five days.[4] We suspect that this residual activity is a remnant of corticoid replacement since the lack of demonstrable stimulation by ACTH tends to rule out the presence of accessory ectopic adrenal tissue.[12] Approximately 5 per cent of administered cortisone is converted to 17-ketosteroid substances, at least 80 per cent of which are devoid of androgenic effect. Theoretically, the androgenic effect of 50 mg. of cortisone is equivalent to about 0.2 mg. of androsterone or about 2 i.u. of androgen.[10] Accordingly, when large doses of cortisone are given, androgen excretion rises in almost a stepwise fashion.[4]

Here we have a most pertinent clinical problem which has yet to be resolved. By suppressing the adrenal cortex with cortisone we often find a remarkable clinical improvement and marked diminution of androgen production.[13-15] Studies of 17-ketosteroids in patients given cortisone for suppression have been equivocal since corticoid metabolites appear in the total 17-ketosteroid determinations.[16, 17] Chromatographic fractionation of androsterone and etiocholanolone suggests a complete suppression of these substances with cortisone administration similar to that effected by adrenalectomy.[18] We are presently carrying out biologic androgen determinations in patients undergoing suppression with cortisone as well as with the newer and more potent steroids such as prednisone and 9-alpha-flourohydrocortisone which, theoretically at least, produce less androgenic metabolites.

5) *Effect of estrogen before and after orchiectomy.* Estrogen therapy has long been used with the hope that in the intact patient, direct suppression of testicular androgen production may result, and, in the orchiectomized patient, suppression of the adrenal cortex would occur. Clinical results treating prostatic cancer tend to indicate that orchiectomy plus estrogen is superior to either alone.[19]

We have recently been making a study of androgen excretion in a group of 40 patients with cancer of the prostate, one group treated by estrogens alone, the other treated by orchiectomy and estrogen administration. The standard medication given was trianisylparachlorethylene (TACE) 12.5 mg. daily. Studies of 17-ketosteroids, 17-hydroxycorticoids, and androgens measured biologically were carried out in all cases. Studies have been completed in 18 patients, 11 intact and 7 castrates; before, during and after estrogen therapy. Of the 11 intact patients, 6 showed definitely less urinary androgen during estrogen therapy (fig. 1). Four patients showed less excretion at times and at other times the diminution was insignificant. One patient showed an increase in androgen, the daily excretion rising from 8.9 i.u. to 23 i.u. per day.

From these data we see that, at this dose, estrogens will produce a definite diminution in androgen production in the majority of older intact patients with prostatic cancer. Although the exact mechanism of this suppression is unknown, experimental estrogen administration is considered to inhibit the pituitary production of gonadotrophin ICSH or LH and hence diminish

[11] Harrison, J. H., Thorn, G. W. and Jenkins, D.: Total adrenalectomy for reactivated carcinoma of the prostate. New Eng. J. Med., **248:** 86–92, 1953.

[12] Graham, L. S.: Celiac accessory adrenal glands. Cancer, **6:** 149, 1953.

[13] Hayward, W. G.: The treatment of late relapse in prostatic carcinoma by cortisone. J. Urol., **69:** 152–156, 1953.

[14] Valk, W. L. and Owens, R. H.: Effect of cortisone on patients with carcinoma of prostate. J. Urol., **71:** 219–225, 1954.

[15] Deming, C. L., Harvard, B. M., Jr. and Sokal, J. E.: Experiences with cortisone in management of far advanced carcinoma of prostate. Tr. Am. Assoc. Genito-Urin. Surg., **46:** 63–75, 1954.

[16] Bonner, C. D., Homburger, F. and Fishman, W. H.: 17-Ketosteroid excretion of patients with and without carcinoma after administration of large doses of cortisone. Cancer, **9:** 234, 1952.

[17] Sokal, J. E., Harvard, B. M., Jr. and Deming, C. L.: The effect of cortisone on 17-ketosteroid excretion of patients with carcinoma of the prostate. Yale J. Biol. and Med., **26:** 345, 1954.

[18] Birke, G., Franksson, C. and Plantin, L. O.: Carcinoma of the prostate: A clinical and steroid metabolic study. Acta chir. scandinav., **109:** 129–149, 1955.

[19] Nesbit, R. M. and Baum, W. C.: Endocrine control of prostatic carcinoma. J.A.M.A., **143:** 1317, 1950.

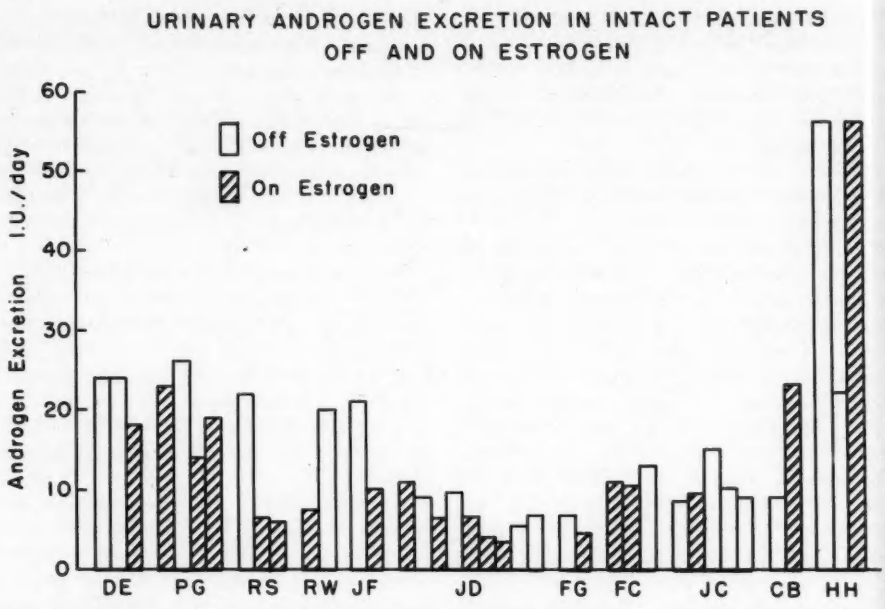

FIG. 1. Urinary androgen excretion of intact patients before and after administration of 12.5 mg. trianisylparachlorethylene for periods of 60 days are shown here. Analysis of figure is given in text.

testicular androgen production.[20] Using a new and rather precise method for the assay of urinary gonadotrophin, we have been able to confirm this in a limited number of intact patients demonstrating a marked reduction in gonadotrophin excretion with high doses of estrogen.[21]

The patient who shows a rise in androgen excretion is interesting from a theoretical point of view since endocrinologists have long postulated that estrogen in high doses increases output of gonadotrophin. This definitely occurs in women, but we have been unable to demonstrate this reversal in the intact male with doses up to 30 mg. daily. Again we have a pertinent clinical problem as the high doses of estrogen advocated by some[22] may, in certain individuals, actually result in increased androgen production although in our current high dose studies we have not encountered this phenomenon.

[20] Christensen, B. G.: Hypofysectomi og Oestrinbehandling. Copenhagen: Munksgaard, 1944.

[21] Munson, P. L. and Parlow, A. F.: Personal communication.

[22] Heckel, N. J.: Endocrine therapy in disease of the prostate gland. Med. Clin. N. Amer., **32**: 111, 1948.

In the orchiectomized group receiving trianisylparachlorethylene the results, surprisingly, were equally impressive (fig. 2). Of the 7 patients, five showed significantly reduced levels of androgen excretion at all times and two showed no significant change. It is of interest that four of the five who showed significant reduction were patients in whom the initial level of androgen was high. The diminution in the fifth patient was statistically significant, even though it represented a rather small reduction in total androgen. Although this is too small a series to support final conclusions, there is a definite further reduction of androgen excretion in the orchiectomized patients as a result of estrogen administration, particularly significant in those with initially high levels of androgen excretion.

Previous clinical studies of androgen excretion in the castrate while on estrogen therapy are at variance. Birke, using fractionation methods, was unable to demonstrate a further reduction of urinary androsterone excretion in 10 orchiectomized patients given doses of stilbestrol as high as 30 mg. a day.[18] In direct contrast, Scott, using a modified fractionation method, found an appreciable reduction in urinary androgen metabolites

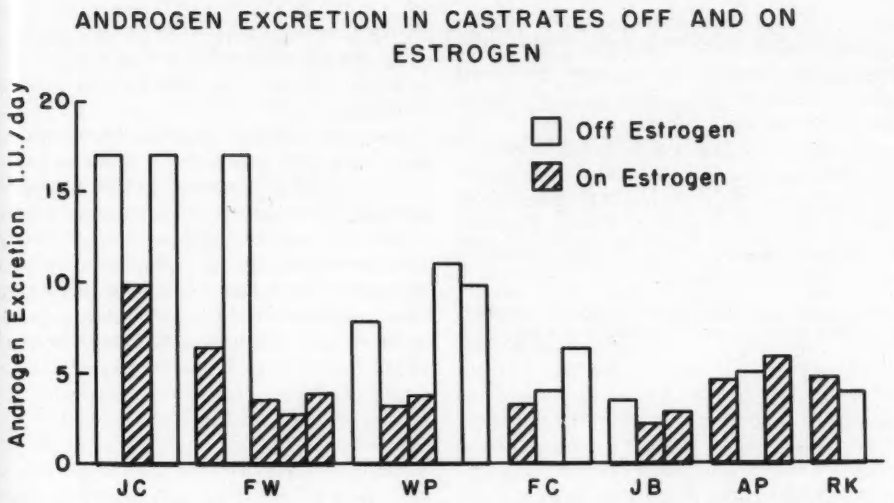

FIG. 2. Changes in androgen excretion in castrates given 12.5 mg. trianisylparachlorethylene daily for 60 days and changes after withdrawal of estrogen. See text for analysis of results.

in 4 orchiectomized patients given only 3 mg. a day.[23] Our findings, using a biologic method, tend to corroborate the latter work and indicate that estrogen does, in fact, seem to suppress urinary androgen excretion in the castrate.

The mechanism by which this reduction occurs deserves brief speculative comment. In the intact patient, androgen production is felt to be reduced by estrogenic suppression of pituitary gonadotrophin as suggested above. In the castrate, however, adrenal androgen production does not appear to be regulated by gonadotrophin; administration of gonadotrophin to orchiectomized patients does not increase excretion of either 17-ketosteroids or androgen metabolites.[10, 23, 24] The adrenal androgen does, however, appear to be stimulated by ACTH. Unfortunately, our present methods of assay for ACTH (which demonstrate elevated levels of this hormone) do not permit evaluation of the normal or low levels we might produce with estrogen administration. Nevertheless, the 17-hydroxycorticoid values of the patients in this study do not show reduction with estrogen administration, suggesting that ACTH suppression is not the mechanism involved. Direct effect on the adrenal is a possibility although the adrenal glands of patients on estrogen therapy for as long as 2 years do not show either gross atrophy or microscopic changes in the zona reticularis to support this concept.[25] Moreover, in the experimental animal, estrogen administration usually results in adrenal hyperplasia.[26-28] We are left then with the presumption that, in the castrate, estrogen in some way alters the natural metabolism of androgens after they are produced by the adrenals.

In addition to the possible suppression of androgen activity, evidence has accumulated to suggest direct suppression of carcinomatous tissue by estrogen,[29-31] as well as inhibition of the

[23] Burt, F. B., Finney, R. P. and Scott, W. W.: Steroid response to therapy in prostatic cancer. J. Urol., **77:** 485–491, 1957.

[24] Heller, C. G. and Nelson, W. O.: The testis-pituitary relationship in man. Recent Prog. in Hormone Research II, p. 229, 1948.

[25] Hertz, R.: Physiologic effects of androgens and estrogens in man. Am. J. Med., **21:** 671–678, 1956.

[26] Burows, H.: Changes induced by oestrogen in the adrenals of male mice. J. Path. & Bact., **43:** 121, 1936.

[27] Ellison, E. T. and Burch, J. C.: Effect of estrogenic substances upon pituitary, adrenals, and ovaries. Endocrinol., **20:** 746, 1936.

[28] Golla, J. M. L. and Reiss, M.: Observations on adreno-corticotrophic action. J. Physiol., **100:** Proceedings 1P, 1941.

[29] Huggins, C. and Clarke, P. J.: Quantitative studies of prostatic secretion. II. The effect of castration and estrogen injection on normal and hyperplastic prostate gland of dogs. J. Exp. Med., **72:** 747, 1940.

[30] Barron, G. E. and Huggins, C.: The metabolism of isolated prostatic tissue. J. Urol., **51:** 630, 1944.

[31] Gaull, G.: Personal communication.

mitotic stimulation produced by certain carcinogens on prostatic tissue.[32] Though not conclusive, these findings suggest that combined castration-estrogen therapy be continued in the initial treatment of prostatic carcinoma. It is our feeling that, when escape from control or reactivation of the tumor occurs, adrenocortical inhibition is indicated, preferably using one of the more active corticoid derivatives such as 9-alpha-flourohydrocortisone which produce fewer androgenic metabolites than cortisone.

[32] Lesnitzki, I.: The effect of estrone alone and combined with 20-methyl-cholanthrene on mouse prostatic glands grown in vitro. Cancer Res., **14:** 632–640, 1954.

SUMMARY

Results are presented of a long term study of androgen excretion in patients with prostatic carcinoma.

The groups studied included young men and older men with and without prostatic cancer. The effects of orchiectomy, ACTH administration and adrenalectomy are noted and discussed.

Androgen excretion is significantly reduced in patients receiving estrogen administration before and after orchiectomy. Continuation of combined castration-estrogen therapy is suggested as the initial ideal hormonal treatment for cancer of the prostate.

TISSUE DISTRIBUTION OF STILBESTROL DIPHOSPHATE: CONCENTRATION IN PROSTATIC TISSUE

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Experience of recent years has proved that hormone treatment of carcinoma of the prostate, although valuable, should be regarded as palliative only. Attempts have been made to extend the period of palliation by using modifications in types and doses of administered hormones (synthetic estrogens and corticoids)[1, 2] and by using operative procedures based on endocrine principles (adrenalectomy and hypophysectomy).[3, 4] None of these methods has advanced this general type of treatment to the curative classification. An additional approach, involving a principle entirely different from endocrine methods, has been to cause a direct cytotoxic effect on carcinomatous tissue. Local instillation of radioactive materials, such as colloidal gold, is showing promising results,[5] but their use is limited and long term curative effects cannot as yet be evaluated. This method depends on the tissue damage inflicted by localized radiation at the site of instillation, but does not achieve homogeneous distribution of the ionized particles in the primary tumor, nor is it of any effect on widespread metastases. A more ideal situation, obviating these disadvantages, would be to destroy cancer cells preferentially by cytotoxic chemicals. Attempts along this line, based on the susceptibility of rapidly growing cells to damage, have not given promising results. A serious disadvantage to this approach has been equal susceptibility of blood forming cells, thus limiting the concentration that can be used. This obstacle could be overcome, perhaps, by utilizing specific biochemical properties of prostatic tissue to cause a localization of administered cytotoxins. In this manner, a tissue-damaging concentration might be confined almost exclusively to the tumor site. Druckrey and Raabe attempted this with the intravenous administration of a water-soluble diphosphorylated ester of diethylstilbestrol.[6] Considering the high levels of acid phosphatase in prostatic tissue, they hoped to achieve a preferential localization of cytotoxic concentrations of the diphosphorylated compound in or close to the cancer cells. This rationale was based on experimental work with sea urchin eggs and with tissue cultures which demonstrated that high concentrations of estrogens have direct cytotoxic influences, including the cessation of mitoses. In a previous publication,[7] we have reported our clinical experience with this compound and have indicated the need for further information with regard to its mode of action, duration of effect, and optimal dosage.

The present study was undertaken to determine the amounts of estrogen recoverable from extracts of human prostate glands following the intravenous infusion of stilbestrol diphosphate. Samples of nonprostatic tissue (fat and muscle) were assayed, also, so that information could be derived concerning the specific concentrating capacity of the prostate gland.

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[1] Smith, P. G., Rush, T. W. and Evans, A. T.: Preliminary report on the clinical use of TACE (chlorotrianisine) in treatment of prostatic cancer. J. Urol., **65:** 886–894, 1951.

[2] Hayward, W. G.: The treatment of late relapse in prostatic carcinoma by cortisone. J. Urol., **69:** 152–156, 1953.

[3] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer; clinical features and urinary excretion of 17-ketosteroids and estrogen. Ann. Surg., **122:** 1031, 1945.

[4] Luft, R. and Olivercrona, H.: Hypophysectomy in man: Experiences in metastatic cancer of the breast. Cancer, **8:** 261–70, 1955.

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[7] Flocks, R. H., Marberger, H., Begley, B. J. and Prendergast, L. J.: Prostatic carcinoma: Treatment of advanced cases with intravenous diethylstilbestrol diphosphate. J. Urol., **74:** 549–551, 1955.

METHODS

Cases selected for this study were patients presenting either benign prostatic hypertrophy or carcinoma of the prostate and were scheduled for prostatic surgery. Stilbestrol diphosphate was administered by intravenous drip with the rate of flow adjusted to 3 drops per second. The material was prepared at a dilution of 500 mg. in 300 cc saline. Surgical removal of the prostate was by suprapubic prostatectomy in most cases, or by transurethral resection or total prostatectomy. Table 1 lists doses prescribed and time intervals between administration of estrogen and surgery. At the time of surgical removal, tissues were weighed and placed in an alcohol-ether solution. Lipid-soluble estrogens were recovered by reflux extraction for several hours, using a soxhlet condenser. In the earlier phases of this study, the residue was then extracted for water-soluble estrogens (presumably unhydrolyzed stilbestrol diphosphate), but this procedure was abandoned when it was realized that these values paralleled those expected on the basis of blood present in the tissue. This situation is due to the fact that the amount of circulating stilbestrol diphosphate remains high for several hours. Therefore, our results express the tissue content of the lipid-soluble estrogens, obtained by alcohol-ether extraction. After evaporation of the solvent, the lipid residue was diluted with vegetable oil, so that 0.5 cc diluted extract was equivalent to 10 gm. tissue. This material, and a series of five 10:1 dilutions, were assayed biologically in immature female mice. Each animal received a total of 0.5 cc during a 3-day injection schedule. Determination of estrogenic activity was based on the weight of the uterus on the day following the last injection. In each assay, standard curves for stilbestrol were established so that the estrogen content of tissue extracts may be expressed as equivalents of stilbestrol per unit weight of tissue. Table 2 summarizes the procedure in this experiment.

TABLE 1

Time Interval*	Dose	No. of Cases
hours	*mg.*	
0–1	1250–2500	5
0–1	1000–500	8
0–1	125–100	5
0–1	100	3
3	1000–500	7
8	1000–500	5
12	1000–500	5
24–48	1000–500	6
Total		44†

* Between beginning of I.V. infusion and surgery.

† 4 cases Ca.; 40 cases BPH.

TABLE 2

I.V. Infusion of Stilbestrol-2 (PO_4)

↓ (Regulated time interval)

Removal of Tissue at Surgery
(Prostate, Fat, Muscle)

↓

Lipid Extraction of Tissue

↓

Dilution of Extract per Unit Weight Tissue

↓

Estrogen Assay in Immature Female Mice

RESULTS

Variation of dose (fig. 1). Within one hour following intravenous doses of 100 mg. to 2.5 gm. stilbestrol diphosphate, assayable estrogens were recovered from extracts of prostatic tissue. With doses up to 1 gm., the quantity recovered was directly proportional to the amount administered. Increasing the dose above 1 gm. did not cause an increase in the tissue concentration of the material. Doses below 100 mg. failed to produce a measurable deposition of estrogen in the prostate, as determined by our methods.

Extracts of fat or muscle from patients who had received 500 mg. to 2.5 gm. stilbestrol diphosphate contained estrogenic activity, but in each of these cases the corresponding prostate-extract had concentrations at least 10-fold greater and frequently 100 times greater. In no instance when less than 500 mg. was infused did the fat or muscle extract contain assayable estrogens. The latter samples were from patients who had received moderate doses of the compound (100 or 125 mg.) and whose prostatic extracts were found to contain significant quantities of estrogen.

Variation of time interval (fig. 2). Assays were done on several prostate-extracts from patients who had not received estrogens prior to surgery. No estrogenic activity was found in these tissues.

When high doses (500 mg. or 1000 mg.) of stilbestrol diphosphate were infused intravenously 1 hour before suprapubic prostatectomy, the lipid-extract of the gland was found to be estrogen-rich, containing an average of 2.5 μg equivalents of stilbestrol per 10 gm. of tissue. With the passing of time, an increase in estrogen content occurred so that glands removed three hours after

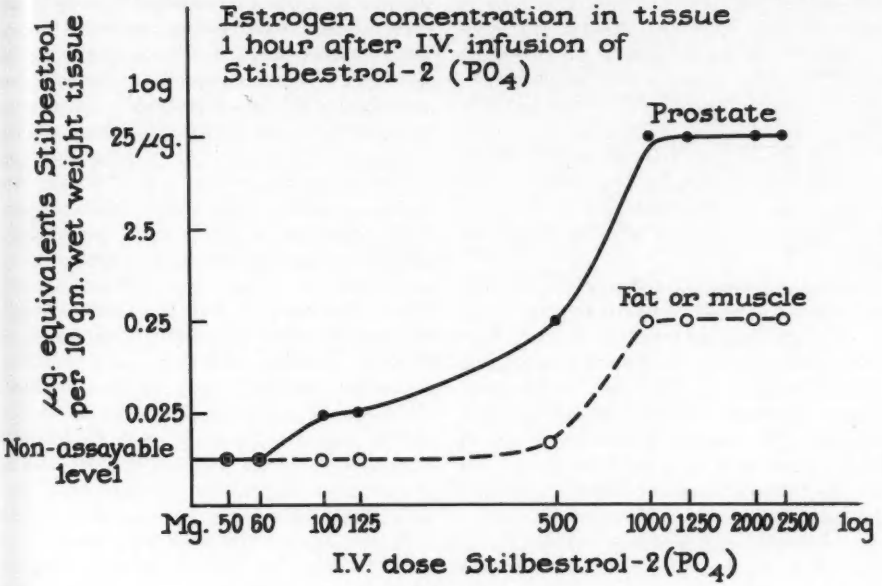

FIG. 1

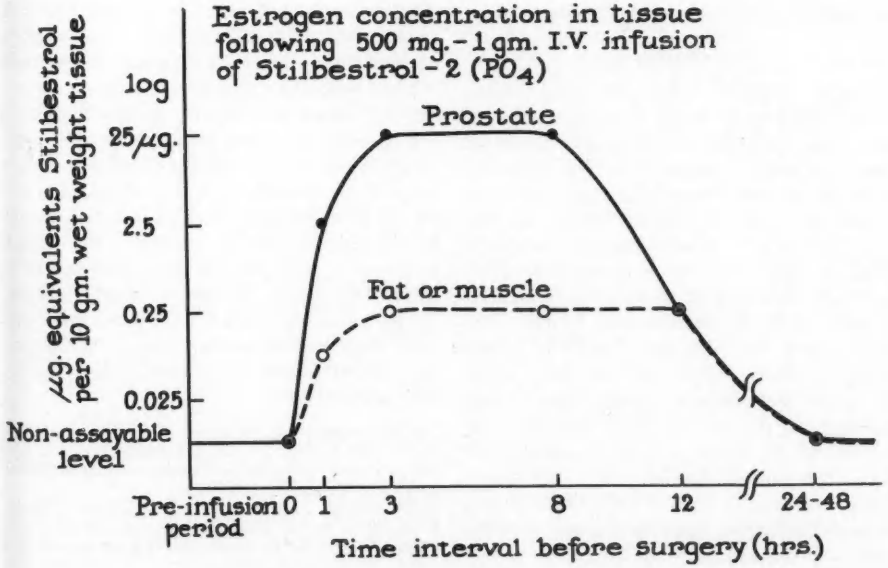

FIG. 2

intravenous infusion of the compound had estrogen values averaging 25 μg equivalents of stilbestrol per 10 gm. of tissue. This 10-fold increase over the level at one hour represented the highest concentration observed. The next time interval tested was eight hours and estrogen concentrations were identical with those at the three-hour interval. Prostates removed after longer periods of time following drug administration had submaximal concentrations of estrogen. At 12 hours the values had declined 100-fold, so that 10 gm. wet weight of tissue contained an average of 0.25 μg equivalents of stilbestrol and at 24 or 48 hours, assayable estrogens were no longer obtained.

Nonprostatic tissue showed approximately the same relation between concentration and time. The concentrations achieved at 3 hours were never exceeded during the 48 hour post-infusion period. A comparison of the two curves shows that as early as 1 hour after infusion of stilbestrol diphosphate, the estrogen content was higher in prostatic than in nonprostatic tissue. At 3–8 hours, the period of maximal difference, prostate contained 100 times as much recoverable estrogens as did equal weights of fat or muscle. By 12 hours, when the prostatic concentrations had started to decline, the concentrations in both types of tissue were essentially equal and by 24 hours neither contained assayable estrogens.

DISCUSSION

Since the synthesis of the water soluble esters of diethylstilbestrol, it has become possible to infuse these compounds directly into the blood to achieve massive circulating levels. This has become an accepted clinical therapy for carcinoma of the prostate in Europe, and to a limited extent, in the United States. As yet no standardization of dosage for this procedure has been offered. On the basis of tissue concentration of estrogens following intravenous infusion, the present study indicates that 1000 mg. is the maximally effective dose and that doses below 100 mg. are ineffective in causing a localization of estrogen in the prostate. Since the estrogens measured in the tissue extracts represent lipid-soluble, free stilbestrol as opposed to the water-soluble vehicular form that was administered, enzymatic hydrolysis might have occurred in the blood, or in the tissues. From the results of this experiment and the known biochemical properties of prostatic tissue, it seems reasonable to assume that dephosphorylation at the tissue level was the major contributory mechanism in liberating free stilbestrol from the diphosphate-ester. As a consequence a transient but significant concentration of estrogen was observed in prostatic tissue as compared with other tissues. The assumption of prostate-specific hydrolysis of the compound is the only reasonable basis on which to account for the higher concentrations found in the gland.

Considering the content of acid phosphatases in various tissues, a high concentration of hydrolyzed stilbestrol in the prostate might be expected, since prostatic tissue is exceptionally rich in this enzyme. In fact, since the enzyme available in the prostate is 1000 times that present in fat or muscle,[8] the 10-fold to 100-fold differences between prostatic and fat or muscle concentrations of estrogen are actually low if one assumes a stoichiometric relationship between tissue content of enzyme and quantity of product formed. It must be considered, however, that not all of the phosphatases measurable by extracting prostatic tissue are actively involved in the metabolic pool in vivo. One must discount the prostatic phosphatases already secreted into the acinal lumen as part of the prostatic secretion. We have recently shown that prostatic tissue, thinly sliced and washed free of stored secretion, contains approximately 1/10th the quantity of enzyme found when determinations are made without separating tissue and stored secretions.[9] When this fact is considered, our observations on estrogen concentrations in fat and muscle versus prostate could result from the differences in tissue content of biologically active phosphatases. If this is true, as seems likely, the basic principle for the clinical use of stilbestrol diphosphate seems to be well-founded. Work utilizing radioactive phosphorus P^{32} as a tracer confirmed selective localization in the prostate but showed even more localization temporarily in the liver and kidney. These factors need further elucidation and study.[10]

[8] Marberger, H., Riedesel, R. D., Anderson, D. O. and Malek, L. H.: A comparative study of phosphatase activities of various human tissues. J. Urol., **75:** 857–864, 1956.

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Our results, however, show that the preferential localization of liberated stilbestrol in the prostate is observable only for 8 hours following the administration of a single dose of the diphosphate ester. This rapid depletion of estrogen content of the prostate indicates that the gland does not possess a storage mechanism which would permit retention of free stilbestrol. The implications of this disadvantage with regard to the clinical effectiveness of the compound are difficult to evaluate and probably are related to the fact that in any given case the therapeutic value of the compound is unpredictable.

It seems unlikely that stilbestrol diphosphate can be expected to act in the role of a cytotoxin precursor, according to the concept of Druckrey and Raabe. If there were some means of trapping and retaining the liberated stilbestrol at the site of hydrolysis, then the higher concentrations of estrogen that would result might be expected to reach the threshold dose for inhibiting mitosis. Nevertheless, the effectiveness of preferential dephosphorylation by the prostate has been demonstrated and our results would seem to justify the search for cytotoxic substances dependent upon this principle for their mode of specific concentration.

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DISCUSSION

DR. WILLIAM WALLACE SCOTT (Baltimore, Md.): I really enjoyed the paper by Dr. O'Conor, because we have worked along similar lines and I was able to understand what he was talking about. (Laughter) May I simply say that, by and large, our results gibe with his.

I want to show two slides which relate to this problem of control following castration relapse. For several years we have been testing steroids in the rat to see what sort of effect they have in the castrate rat whose prostate is made to grow again with androgenic substances.

[Slide] This is our method of test. These animals are all castrated animals who received testosterone propionate in the dosage shown. In addition to that, they received the compound under test. I would like to show you the most recent data from the National Cancer Chemotherapy Service Center in Washington using an identical test and evaluating the corticoids about which Dr. O'Conor spoke.

[Slide] This slide shows the anti-androgenic action of these four corticoids against testosterone propionate in the rat. We see here that prednisone is most active, cortisone next, cortisol next, and prednisolone next. Diethylstilbestrol would rate between cortisol and prednisolone, and yet for my money diethylstilbestrol is a better drug in the treatment of the patient with prostatic cancer who has relapsed after castration than most of these corticoids.

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): This contribution which we have just heard is a milepost in assisting us to comprehend what happens in the general metabolic pattern of patients with prostatic malignancy.

There are certain aspects of steroids and endocrines which are of enough interest to comment on.

First of all, the late Dr. Engle observed that estrogens are actually capable of and are being elaborated in peripheral tissues. In addition to that, we know that when we introduce into a woman large doses of estrogens, the estrogen excretion, rather than being increased, is sometimes diminished. It is also a clinical observation that estrogen is sometimes increased following the administration of androgen.

It has also been observed in the basic biochemical reactions that take place in inflammatory areas that the growth hormone is elaborated during the process of the mechanism of inflammation.

These facts are some of the complications in this problem which we are trying so hard to understand.

Some aspects of this contribution are valuable in supporting the policy of not bombarding a patient who has prostatic cancer with estrogens.

As we have added to our knowledge of these basic chemical combinations and patterns, and as we become more aware of the specific action of enzymes in individual cells in their relationship to the elaboration of all these substances, then we will be much more capable of intelligently managing these problems.

Enzymes actually are the substances which elaborate all of our endocrine substances in the body as well as in the pharmaceutical laboratories.

Again I should like to reiterate a feeling which I have had since 1940, that in the management of prostatic malignancy whatever we see fit to administer in the way of therapeutic agents is prescribed in the smallest clinically effective dose.

DR. VINCENT J. O'CONOR, JR. (Boston, Mass.): I would like to say a word about Dr. Flocks' work. We feel that even though we have shown a definite androgen-suppressing effect of estrogen given in particular to the orchiectomized patient, a lot of data are accumulating to show that estrogen does in fact have a very definite *direct* effect on prostatic tissue.

In conjunction with the work which Dr. Huggins did originally, there are several studies going on at the present time using enzyme systems as the method of study. I would like briefly to show you one which is being used.

[Demonstration on blackboard.]

This is an enzyme system that is fairly complex but which we feel gives a fairly accurate reflection of the inherent metabolism of the cell particularly with regard to fresh prostatic tissue.

Here is an isocitric cycle, plus DPN, to which we add the substrate here, and end up measuring the 2-ketoglutarate which is formed. So far in the preliminary work, taking fresh prostatic

tissue, normal, hyperplastic and carcinomatous, and putting that in at this level or studying it at this level with estrogen, we have just now begun to accumulate data suggesting that there is, in fact, a greater effect of estrogen on the carcinomatous tissue than there is in the hyperplastic tissue.

In addition to this, studies have shown that estrogen will diminish the effect of certain carcinogens, 20-methylcholanthrene, for example, in the isolated mouse or rat prostate; in other words, estrogen diminishes the carcinogenic effect of these drugs. These data tend to support the theory that estrogen probably in some way does have a direct effect on the carcinomatous tissue.

We agree definitely with Dr. Herbst that increased doses might conceivably be detrimental. We are presently carrying out what we call high dose studies in an attempt to confirm the work of Dr. Birke in Stockholm, in which he used doses of 5 mg., 10 mg. and 30 mg. showing that for a complete suppression of androgen, as measured by his fractionation method, which actually shows pure androsterone, using 5 mg. stilbestrol it took him 30 days to get complete suppression. Using 10 mg. it took him ten days. Using 30 mg. a day he could suppress all androgenic function in a matter of three days.

It is our feeling that with an initially high loading dose for three to five days we can maintain a patient on either 5 or 10 mg. stilbestrol a day.

Dr. Rubin H. Flocks (Iowa City, Iowa): I just want to thank the discussers, especially Dr. O'Conor, for his kind emphasis of the point that I really wanted to make, namely, the utilization of the specific properties of prostatic tissue for altering its growth. The work described simply was one of the experiments trying to attack the prostatic disease upon this basis.

REPLACEMENT OF THE URETER BY SMALL INTESTINE: CLINICAL APPLICATION AND RESULTS OF THE "ILEAL URETER"

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In a previous paper with Vincent Moore and others (1956), we reviewed the historical background of the use of isolated segments of ileum for ureteral repair and described early clinical experience with the first four patients in whom we had tried the procedure. A great deal has been written about experimental and clinical application of this procedure. The papers of Annis (1953), Bitker (1954), Baum (1954), and Goldstein and associates (1956) review the pertinent literature quite completely. Wells (1956) reported 56 cases in which the ileum was used for ureteric replacement in the collected experience of members of the British Urological Association. There have been several favorable reports on this subject in the American literature (Baum; Davis and Nealton; DeWeerd and Reno; Moore and others; Pyrah, '57; Swenson and associates; Ulm). It seems well-established as a useful and safe procedure in selected cases.

Some urologists have been reluctant to employ the ileal ureter, however, possibly because of unfamiliarity with handling the small bowel. Now that the "Bricker procedure" for permanent urinary diversion to the skin by ureteroileocutaneous anastomosis is finding wide favor and application, it is likely that ureteric replacement by ileac segments will find wider acceptance. It may be helpful to think of this procedure as like "Bricker's operation" with anastomosis of the ileac stoma to the bladder instead of to the skin.

The purpose of this report is to describe experience and lessons learned to date from a collected series of 16 patients in whom ureteral replacement with an isolated ileac segment has been employed by members of the staff of the Department of Surgery, University of California Medical Center, Los Angeles. Figure 1 shows in diagrammatic form the various anatomical situations involved.

Animal research basic to this work was supported by the Bay District Surgical Society and the Fund for the Advancement of Urology.

INDICATIONS

The certain indication for use of the ileal ureter is damage or loss of the normal ureter with no chance to use the urinary tract for reconstruction. Burns has properly emphasized the importance of early conservative repair of ureteral injuries, and Ockerblad and others have described the use of flaps of bladder to bridge lower ureteral defects.

In our opinion, available tissues of the urinary tract should be used for ureteral repair whenever possible. This includes reanastomosis of a severed ureter, bladder flap operations to bridge lower ureteral defects, and transureteroureterostomy when feasible.

However, there are some unfortunate patients suffering with the discomfort and inconvenience of obligatory nephrostomy due to irreparable ureteral defects. These are candidates for the ileal ureter. Most of these patients are women with severe urological complications following extensive pelvic surgery for cancer (cases 1–4 and 10–15).

We have not yet used the following procedure but believe that it represents a reasonable plan of action in the occasional patient with loss of both ureters following Wertheim's operation: Stage 1 of restorative surgery should be Bricker's operation, ureteroileocutaneous diversion of urine. Then, after damage from pelvic abscess and urinary extravasation is healed, the cutaneous ileal stoma could be re-transplanted to the urinary bladder.

In only one instance have we employed the ileal ureter to treat vesicoureteral reflux and megaloureter. This procedure failed in case 7 because of excessive length of ileum and the fact that the bladder did not function normally. Except in the experimental animal, we have not yet tried Swenson's recommended technique of tailoring the ileum to make a smaller-sized segment which acts as a urinary conduit. The results of ureteral replacement with segments of

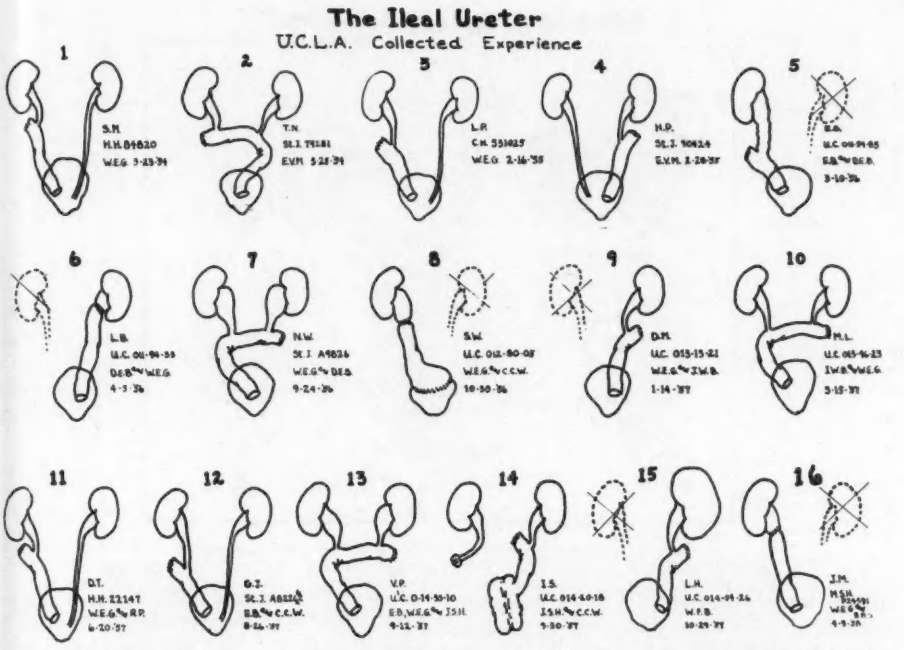

FIG. 1. Replacement of the ureter by small intestine, U.C.L.A. collected experience, March 1954 to April 1958.

ileum are so satisfactory in general that it does not seem necessary to adopt this more complicated technique.

TECHNIQUE

In our previous paper, the technique is described and illustrated in detail; however, a few important points need to be stressed (fig. 2).

1) The ileac segment should be as short as is reasonably consistent with the need, rarely more than 25 cm. Too long a piece of bowel may predispose poor drainage and cause uremia and acidosis (case 7).

2) The portion of ileum used should not be isolated too close to the ileocecal valve. The optimum segment is probably at least 20 cm. or more from the cecum. This is important as the terminal portion of the segment and its mesentery has to be brought down to the bladder for anastomosis.

3) Several different anatomical arrangements have been employed by various surgeons reporting their work (fig. 3). It seems clear that the flow of urine should always be in an *iso*peristaltic direction (Davis and Nealon).

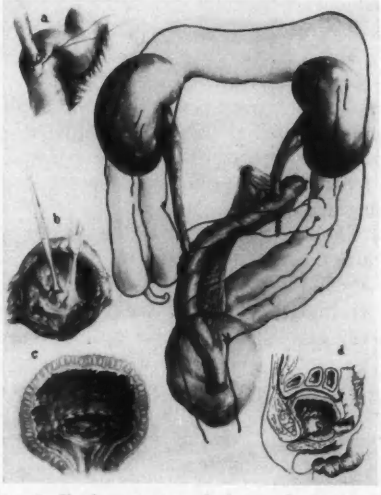

FIG. 2. Ileal ureter; technique of anastomosis. See text on technique.

4) The ureteroileac anastomosis is done as in Bricker's operation, usually with two layers of sutures; catgut is used. *No* silk is used in the

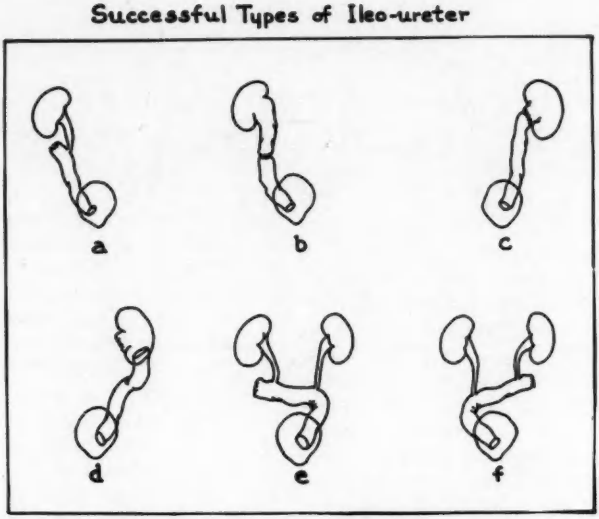

FIG. 3. Types of ureteral replacement by ileal segments

urinary tract, although it is favored for the ileoileostomy which must be done after isolation of the segment of bowel (fig. 2, *A*).

5) Splints may or may not be used, depending upon the preference of the surgeon. They undoubtedly add a safety factor.

6) Sites of anastomosis should be drained.

7) The ileal segment may be anastomosed to the renal pelvis (cases 6 and 16). When there is a pre-existing nephrostomy, it is very helpful to pass a long curved clamp into the renal pelvis through the nephrostomy sinus and thus locate the renal pelvis from inside the peritoneum by finding the tip of the clamp.

8) The ileal ureter may be made to lie either inside or outside (cases 9 and 16) the peritoneum (Moore and associates; Ulm). There is probably no advantage to placing the ileum retroperitoneally, and the extra trouble involved is usually not warranted. When the ileum lies intraperitoneally, care should be taken to prevent herniation of bowel behind the mesentery. This is accomplished by fixing the mesentery of the segment to the retroperitoneum.

9) The ileovesical anastomosis should be made as low as possible, on the back of the bladder and near the trigone in the fixed portion of the bladder (fig. 2, *D*).

10) When the distal end of the ileac segment is anastomosed to the bladder, it is important to *cut out a window* of bladder tissue, thus preventing late stenosis of the stoma (case 6) (fig. 2, *B* and *C*).

11) It is easier to do the ileovesical anastomosis from *inside* the bladder.

12) Appendectomy is done at the same time if the appendix is still present.

RESULTS

Good: Cases 1, 2, 3, 4, 9, 10, 11, 12, 13, 15, and 16.

Fair: Case 5.

Poor: Case 6.

Failure: Cases 7, 8, and 14.

Complications, early: Cases 13 and 16.

Complications, late: Cases 1, 2, 5, 6, 7, 8, and 14.

Death related to surgery: None.

Some of the complications which have been observed are as follows:

Case 1. Although the end result is nearly perfect anatomically, the patient complains of intermittent nocturnal incontinence. This may represent peristaltic activity of the loop of ileum which causes intermittent overflow. She is not incontinent in the daytime (fig. 4).

Case 2. In this patient late stenosis of the right ureteroileac anastomosis developed three and one-half years after the original surgery (fig. 5). The area was re-explored because of progressive

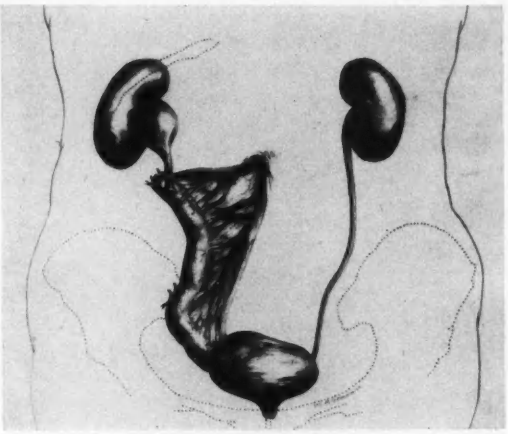

FIG. 4. Case 1. Anatomical arrangement

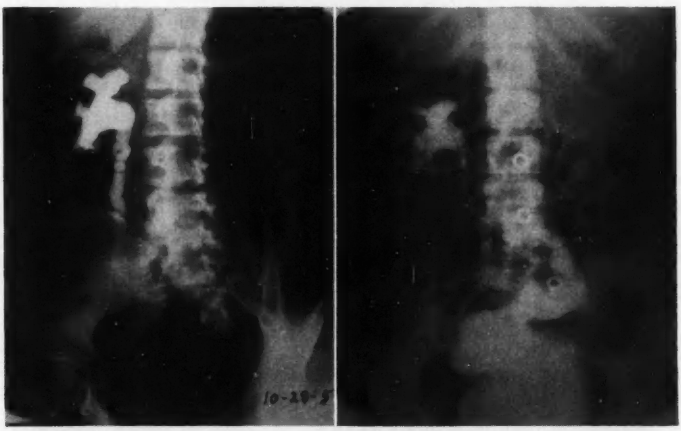

FIG. 5. Case 2. Bilateral ureteral replacement. Stenosis developed at right ureteroileal anastomosis, 3½ years after original surgery. Reimplantation was performed.

hydronephrosis and pain. The cause of stenosis was not determined. Reanastomosis was performed, and a redundant loop of the segment of ileum was removed. It is interesting that this bowel tissue which had been in contact with the urinary tract for over three years appeared the same as normal bowel under the microscope (fig. 6).

Case 5. In this patient, who had a solitary kidney and poor renal function, uremia and acidosis developed which were reversible. Apparently this was due to reduced renal reserve and a too short segment of ileum which did not prevent reflux (fig. 7). This ceased with catheter drainage.

Case 6. In this patient, who had a solitary kidney and an obligatory nephrostomy after multiple operations on the ureteropelvic junction, late obstruction of the ileovesical anastomosis developed and on two occasions necessitated reoperation. This is attributed to the fact that no window was cut out of the bladder at the time of ileovesical anastomosis. She also had too long an ileal segment which later had to be shortened (fig. 8).

Cases 7 and 8 failed and had to be converted

to ileocutaneous anastomoses because of initially poor renal function coupled with retention of urine and development of uremia and acidosis due to absorption.

Table 1 shows changes in the blood chemistry determinations in patient 8 who had a solitary kidney with severe renal damage due to tuberculosis. It was necessary to interrupt the ileal

FIG. 6. Case 2. Segment of ileal ureter removed after being part of urinary tract for 3½ years. Note normal appearance of ileum.

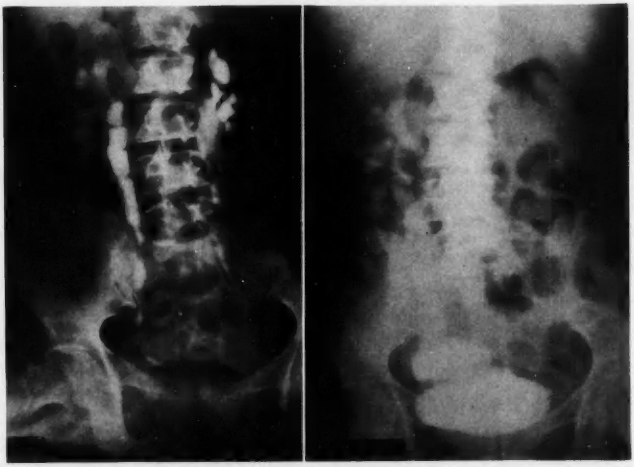

FIG. 7. Case 5. *A*, preoperative. *B*, postoperative. Note short ileal segment and end-to-end anastomosis of ureter to ileum. Left kidney was removed.

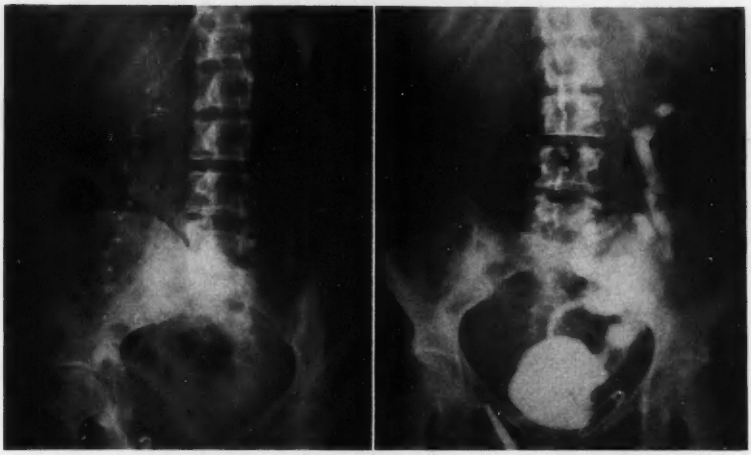

FIG. 8. Case 6. Ileal segment is too long, and obstruction occurred at ureterovesical anastomosis because no "window" was cut in back of bladder.

TABLE 1. *Case 8 (failure). Uremia and acidosis aggravated by urinary absorption and poor renal reserve. Situation was improved when closed system was interrupted and urine diverted to skin (ureteroileocutaneous anastomosis). Patient had solitary right kidney with advanced damage due to tuberculosis. Died of uremia 1½ years later*

Dates	NPN	BUN	CO_2	Cl	Na	K
December						
3	76.1		22.0	100.0	136.9	4.1
7	68.4		17.4			
11	87.5		16.2	100	137.5	5.74
January						
7	117	87 (specimen stood overnight)	11.5	103.7	138.2	3.92
8	118		12.8	110.7	139.2	4.27
9	111.0		4.8			
10	129	80	12.8	109.9	132.7	3.98
11	102	74	13.6	106.3	126.7	3.84
12	102		12.4	104.5	134.2	3.31
12 OPERATION. Abdominal exploration; *interruption of ileal ureter; ileocutaneous anastomosis*						
14	99	75	19.1	103.6	140.2	3.63
15	114	83.2	22.5	105.4	141.5	3.57
16	109	78	19.1	98.1	136.0	4.29
17	114	83	22.5	100.0	134.0	4.62
19	98		26.7	100.0	137.9	5.78
22		56				
28		50				
30	55	38	26.7	94.5	132.6	5.7

ureter and bring it to the skin. There was a decrease in the uremia and improvement of acidosis after this was done.

Case 13. A leak developed at the point of ureteroileal anastomosis due to a puncture in the ureter at the time of surgery. This necessitated reoperation and temporary T-tube drainage of the wound (figs. 9 and 10).

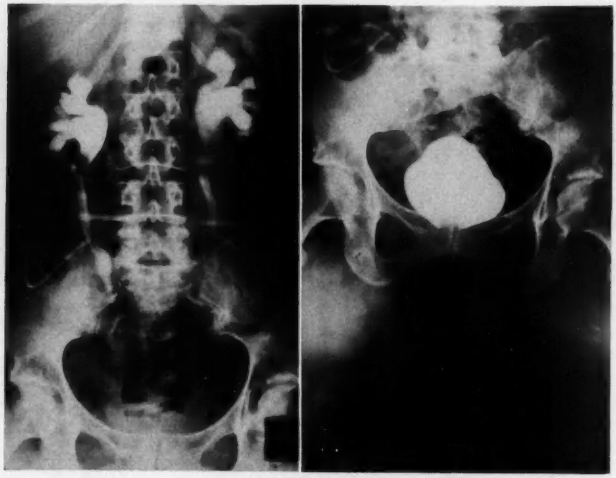

FIG. 9. Case 13. Preoperative study. Bilateral obligatory ureterostomy after radical pelvic surgery and loss of both lower ureters.

Case 14. This procedure failed because of a vesicovaginal fistula which became evident after surgery. This fistula was actually present, though unrecognized, before the procedure was performed. This emphasizes an important caution, that the urinary bladder should be carefully studied in these patients before re-establishing normal continuity of the urinary tract. If a fistula is present, of course, it is much more difficult to repair after there is urine in the system. In this particular patient, a small contracted bladder was enlarged with a segment of sigmoid colon. This produced a satisfactory technical result, and the ileal ureter was anastomosed to it. However, the fistula persisted and the end result was cutaneous ureteroileostomy from the solitary good kidney. It is important to demonstrate normal bladder function before re-establishing use of the lower urinary tract in patients with severe urinary tract damage after pelvic surgery for cancer.

Case 16. This man had multiple obstructing papillary carcinomas of a solitary right ureter. His condition was complicated by severe, advanced arteriosclerosis. Ureterectomy and substitution of an ileal segment from renal pelvis to bladder (as described by Pyrah) were technically satisfactory and probably curative. During the first postoperative week, impending arteriosclerotic gangrene developed in the right leg. This finally resolved, and early results are encouraging. He has not been followed long enough to be certain of the ultimate result.

FIG. 10. Case 13. Postoperative study

Encouraging lessons which have been learned are as follows:

Case 3. This young woman lost both lower ureters secondary to Wertheim's operation for cervical cancer. The left side was repaired by a bladder flap type of procedure, but the same procedure failed on the right. There was a debate

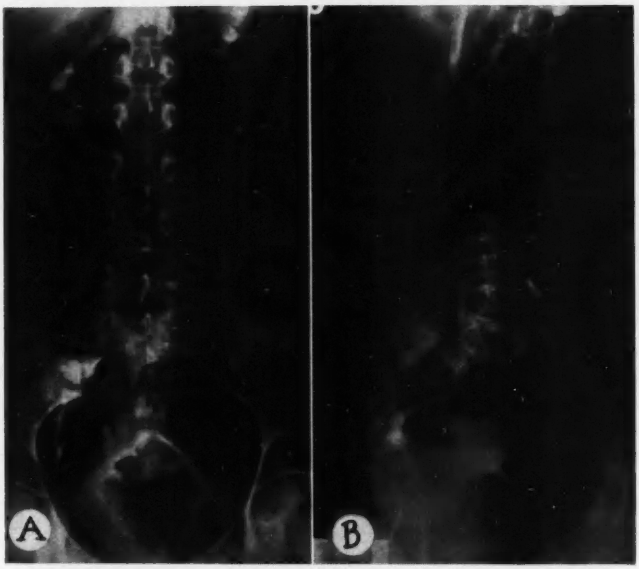

FIG. 11. Case 3. *A*, right ileal ureter. Left "bladder flap" operation. *B*, oblique film

as to whether to perform right nephrectomy and leave her with a solitary left kidney or whether to try to re-establish the normal right urinary tract continuity. The latter course was elected, and the ileal ureter was used with good results (fig. 11). Late observation reveals that the patient now suffers with pain and intermittent pyelonephritis in the *left* kidney which was the side in which the bladder flap operation was successful. What was formerly thought to be her "good" kidney is now turning out to be her "bad" kidney. It is worthwhile to preserve a good kidney even if the other side appears at first to be normal.

Case 9. A 16-year-old boy had congenital anomalies consisting of vesical neck obstruction, bilateral vesicoureteral reflux, and bilateral hydronephrosis. The right kidney was only a nonfunctioning shell. Previous surgery had removed the vesical neck obstruction and produced a good functioning bladder. An attempt had been made to eradicate upper ureteral obstruction and remove a redundant upper portion of the left ureter. This failed and ended with permanent damage to the upper third of the left ureter. There was no way of reanastomosing this to the lower urinary tract except the possible use of transureteroureterostomy which would not have been good in this case because of reflux. The patient had an obligatory nephrostomy and had also developed calculi in the lower calyx (fig. 12, *A* and *B*). At surgery, the functionless right upper urinary tract was removed, and the remaining left ureter which was acting as a diverticulum due to reflux was also removed. In each case, transvesical ureteral intussusception was employed with ease. The ileal segment was then attached to the lower portion of the left renal pelvis and brought extraperitoneally to the bladder. After suitable healing, the nephrostomy tube was removed. The nephrostomy wound closed rapidly and the patient made a normal and speedy recovery (fig. 12, *C* and *D*). Blood chemistry studies have remained normal, although the nonprotein nitrogen is slightly elevated as it was formerly. It was determined in this case that this would be done as a trial procedure, because it followed the bitter experience of having failed in case 8; it was feared that renal function might be too poor to assume success in this case. However, the end result in over a year of followup is extremely satisfactory. It is of considerable interest that the stones which lay in the lower calyx of the solitary kidney have apparently disappeared, either by spontaneous

dissolution or by being passed down the ileal ureter without the knowledge of the patient.

Case 15 was performed by Dr. Wiley Barker, one of the general surgeons on our staff. His patient had a congenital solitary left kidney and recurrence of a hugh incurable cancer in the left portion of the bony pelvis. Operation was done as an emergency because the lower bowel perforated due to obstruction. At surgery, he removed the whole necrotic, neoplastic mass and re-established normal continuity of the lower bowel. He found that the solitary left ureter was hydronephrotic and involved in the neoplasm. It had to be removed at the same time. This left him with three possibilities: 1) cutaneous ureterostomy, 2) nephrostomy, and 3) employment of the ileal ureter. He elected the latter and performed this as an additional procedure to re-establish normal continuity of the urinary tract. The end result is excellent from a functional standpoint, although, of course, the patient is not cured of her neoplasm. This demonstrates the usefulness of this procedure in the hands of skilled general surgeons who may, of necessity, find themselves with the need to replace a damaged ureter.

It is our impression that in general the strong peristalsis of the ileac segment protects the kidney from ill effects or reflux, even though there is some reflux when the bladder is full as demonstrated by cystogram on most of these patients. These studies have been confirmed by cinefluorographic observations in some cases. When the pressure in the bladder is raised, it is transmitted to the ileac segment and ultimately to the kidney. This has been tested in two patients (cases 4 and 13) and recorded as cystometric and nephrometric studies (figs. 13 and 14).

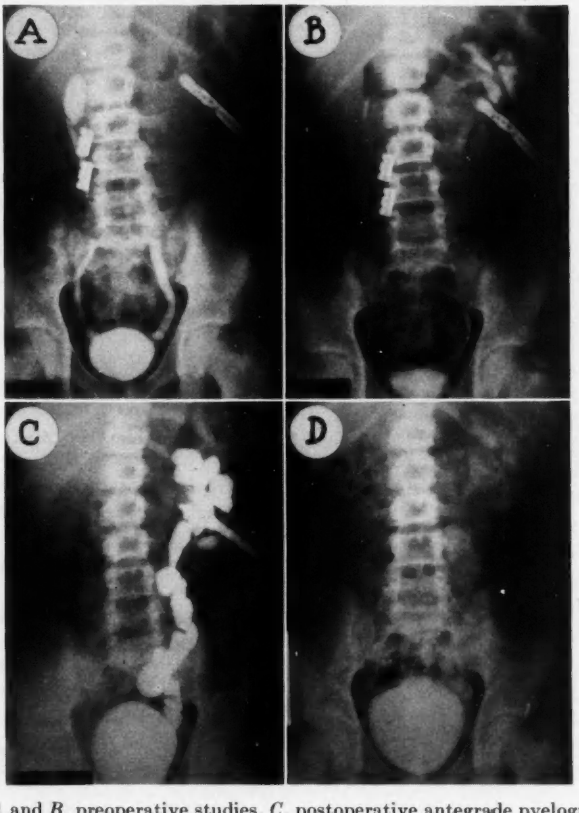

FIG. 12. Case 9. *A* and *B*, preoperative studies. *C*, postoperative antegrade pyelogram. *D*, postoperative intravenous pyelogram.

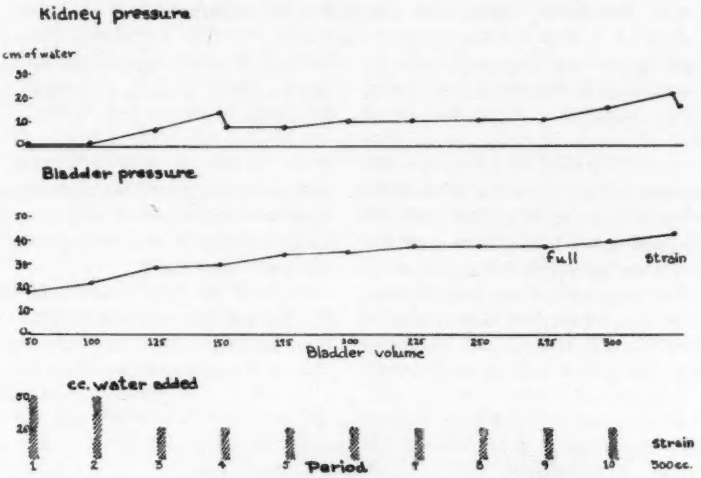

FIG. 13. Case 4. Combined cystometric and nephrometric study

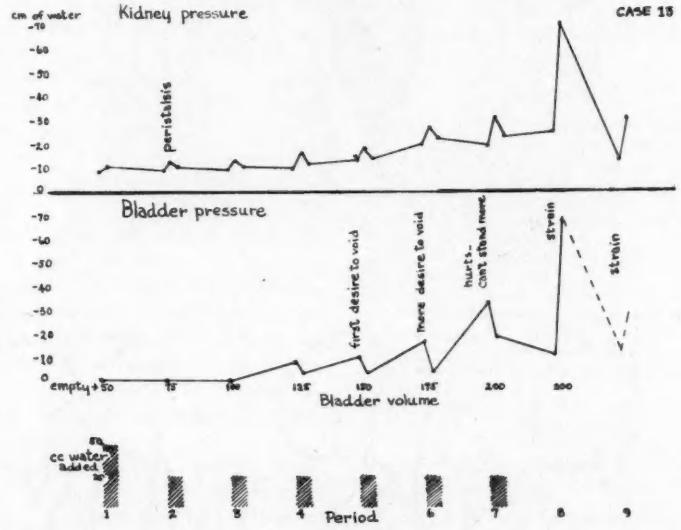

FIG. 14. Case 13. Combined cystometric and nephrometric study. Note that pressure in the ileal ureter rises as pressure and volume in the bladder are increased.

A word should be said about the site of ureteroileal anastomosis. Should it be end-to-end or end of ureter to side of ileum? We have employed both with good results. However, although absolute proof is lacking, we believe that end-to-side anastomosis is better in preventing reflux. As well, we believe that the minimal length of ileum should be not less than 15 cm. to ensure the beneficial effects of peristalsis to prevent renal damage.

SUMMARY

Results and lessons learned from 16 patients in whom isolated segments of ileum were used to

bridge ureteral defects are presented. Complications are enumerated. Technique is briefly discussed and illustrated.

CONCLUSIONS

Replacement of a damaged ureter by isolated segments of small intestine is feasible and safe in properly selected cases. It should be employed as a last resort when use of normal tissues of the urinary tract is impossible. Complications may accompany this type of surgery, but in general it is a safe and useful procedure. It should be used by choice with proper indications to restore continuity of the upper urinary tract when no other method exists and the lower urinary tract is normal.

ADDENDUM

Since this paper was presented, two more cases have been added; and a longer term followup on case 16 is now available. The result in this case is perfect.

Case 17 (fig. 15). Mrs. E. R. (UC No. 015-44-46), a 42-year-old woman, had bilateral staghorn calculi, with severe infection. She had a history of one operation on the left side and two

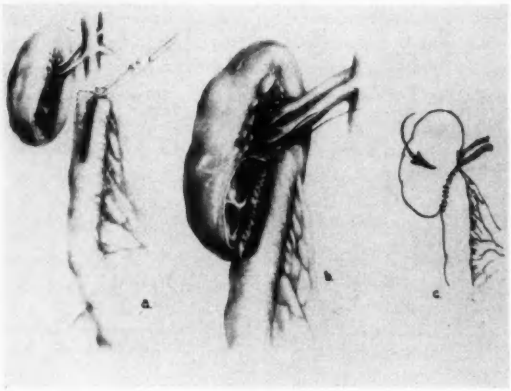

FIG. 15

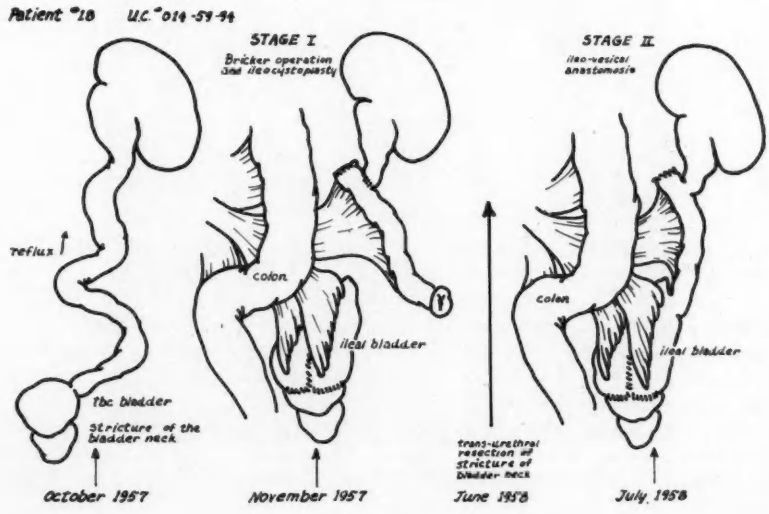

FIG. 16

operations on the right side, with recurrence of calculi. The right pyohydronephrosis with obstructing calculus was a source of pain and fever. There was a persistent stricture at the right ureteropelvic junction, with severe scarring from previous surgery.

On May 23, 1958, the operation (fig. 16) was carried out, together with removal of the obstructing staghorn calculus and the strictured ureter. The lower pole of the right kidney was split medially from the pelvis to the lowermost calyx and the stone removed. The isolated ileal segment was attached by direct anastomosis to the pelvis and calyces of the lower portion of this kidney (pyelo-caliceal-ileal anastomosis). The other end of the ileal segment was attached to the bladder. The postoperative course was complicated by a wound infection, but healing was satisfactory, and the patient has an excellent postoperative result. There has been improvement in the function of the damaged right kidney, and there is good drainage. It is too early to be certain, but it would seem impossible for a further stone to form and remain in the kidney with the large caliber drainage afforded by the ileal segment. If long-term observation of this situation confirms present optimism concerning the result, the same procedure will be repeated on the opposite side at a later date.

Case 18. The events of this patient's urological history and the use of the ileal ureter are shown diagramatically in figure 16. Mr. H. W. (UC No. 014-59-94) is a 56-year-old man with a life long history of tuberculosis. In 1937, the right kidney was removed for renal tuberculosis. Subsequently, tuberculous cystitis and a contracted bladder developed and left hydronephrosis and reflux. He first came under our care in October 1957 with severe left hydronephrosis, azotemia, and constant urination for which he was wearing an external urinal.

In November 1957, an ileal segment, 40 cm. in length, was isolated and divided into two portions. The upper portion was used for Bricker's operation, to give the patient a left ureteroileocutaneous anastomosis. The lower portion was formed into a cup-like structure and anastomosed to the contracted tuberculous bladder (ileocystoplasty). This left a defunctionalized ileal bladder. It was decided to manage this temporarily in this staged fashion because of the patient's azotemia.

Postoperative course was uncomplicated and the patient enjoyed a smooth convalescence.

In June 1958, transurethral resection of the contracted bladder neck and stricture caused by the old tuberculous cystitis and prostatitis was carried out. Following this, it was possible to fill the ileal bladder with 250 to 300 cc irrigating fluid. A test was made to see if the patient could tolerate having his urine go into this bladder by taking all the urine from the Bricker ileostomy appliance and putting it into the bladder for a period of two weeks. The patient did not seem suffer from this, and accordingly in July 1958, the cutaneous anastomosis was taken down and relocated by direct anastomosis to the upper portion of the ileal bladder, restoring uninterrupted continuity of the urinary tract.

So far, he tolerates this situation well. Bladder capacity is 350 cc. It is still too early to be certain whether or not he will be able to manage without later cutaneous diversion. This will depend on the degree of reabsorption from the large segment of ileum in the presence of moderately reduced renal function. Early results of this procedure are technically satisfactory, and the patient is well-pleased.

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URETERONEOCYSTOSTOMY

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Reimplantation of the ureter into the bladder is a common surgical procedure that has been performed many hundreds of times, yet has not been reported in the literature as often as one would expect. Since ureteroneocystostomy is often a palliative measure in the treatment of carcinoma of the bladder, long-term postoperative study has not been possible in many cases. Another reason, of course, has been the unpredictable and generally indifferent results that sometimes follow this procedure. In spite of considerable experimental work and the development of numerous surgical techniques, an entirely satisfactory method of anastomosis has not yet been achieved.

Two significant series of ureteroneocystostomies have been reported in the literature of the past 20 years. Henderson has reviewed 73 cases of reimplantation of the ureter in England with good postoperative followup study in about one-half of the patients. Sixty-seven of the ureters were transplanted at the time of partial cystectomy for carcinoma of the bladder. Stevens and Marshall have reported a series of 10 ureteroneocystostomies that were done during segmental resection of the bladder for carcinoma. They used a method of submucosal oblique implantation that prevented reflux in some of the patients. Dodson has reviewed the history of ureteroneocystostomy and described a technique of implantation that we have modified and used in 12 cases. During the past 5 years we have done ureteroneocystostomy 28 times. Intravenous pyelograms were made in each of the cases at periods from 2 months to 5 years postoperatively and cystograms were made in half of the patients. All the patients have been seen at 3 to 6 month intervals so that a fairly accurate evaluation of urinary tract infection has been made. Five patients with carcinoma of the bladder died during a period of 6 months to 2 years following surgery.

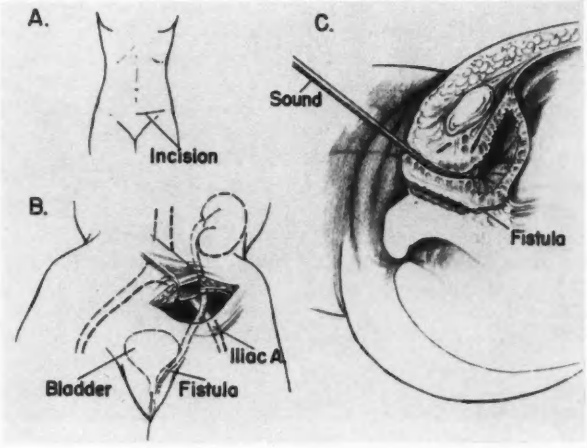

FIG. 1

The indications for ureteroneocystostomy were: ureteral injury following gynecological surgery in 15 patients; segmental bladder resection for carcinoma involving a ureteral orifice in 10 cases; ureteral stricture from calculus manipulation in 2 patients; and ureteral ectopia in 2 cases. Three methods of ureteroneocystostomy were used in the 28 cases reported. In 12 patients a modified pull-through technique described by Dodson was used and we will refer to this technique as the

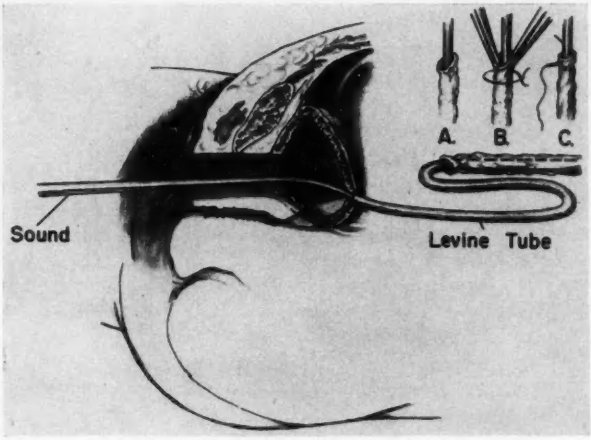

FIG. 2

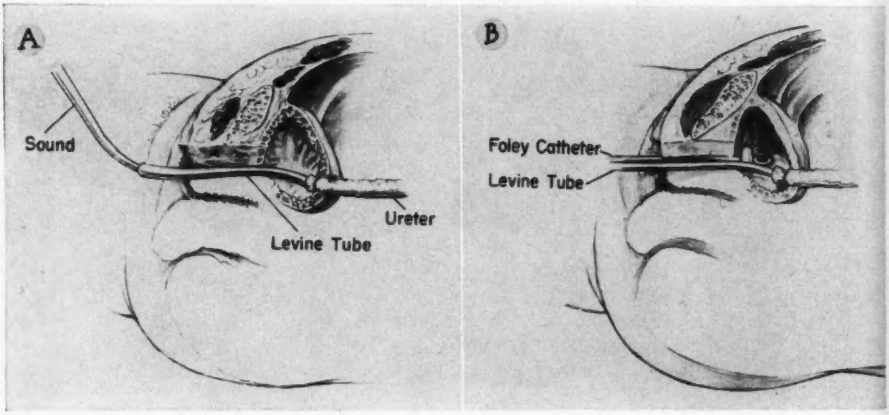

FIG. 3

"closed method." A low transverse extraperitoneal incision is made down through the abdominal wall to the ureter. The ureter is then dissected from the scarred area and freed sufficiently so that adequate length can be obtained. As much blood supply as possible is left intact, although at times it has been necessary to denude as much as four inches of ureter from its segmental blood supply without ill effects. A size 8 or 10F soft rubber Levine tube is then passed up the ureter to the pelvis and a fine plain catgut suture is tied around the distal end of the ureter to hold the tube in place (figs. 1–3). A size 20F steel sound is then passed through the urethra to the bladder and a convenient area for an anastomosis is found. A small incision is made

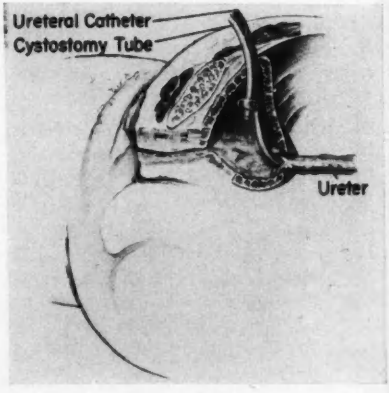

FIG. 4

over the sound and the sound is passed through it. The end of the Levine tube is then fitted over the end of the sound and the sound is withdrawn from the bladder and urethra carrying the Levine tube out through the urethra. Two or three fine chromic catgut sutures are then placed through the adventitia of the ureter and the wall of the bladder and a Penrose drain is left down to the site of the anastomosis. The abdominal wall is then closed. A size 24 Foley catheter is left in the bladder under mild tension and the Levine tube is attached to it. A cystostomy has not been done in any of these cases. Antibiotics were used freely, and the Levine tube, which not only splinted the ureter but also drained the kidney, was left indwelling for a period of 12 days. Although in some cases as much as a centimeter of ureter was drawn into the bladder, the redundant portion eventually sloughed, and cystoscopically only a normal-appearing ureteral orifice could be seen which opened and closed during peristalsis. Passive and voiding cystograms were made in 6 of these patients and reflux occurred in only 1 patient. Pyelonephritis occurred in four of the 12 patients 2 to 6 weeks postoperatively, but did not occur in any of the patients after 3 months. Five of these patients had normal intravenous pyelograms; 6 had 1 plus hydronephrosis; and 4 had 2 plus hydronephrosis postoperatively. One patient had normal pyelograms until 3 years postoperatively and then 1 plus hydronephrosis developed, undoubtedly due to reflux. The ease of operation was dependent largely on the time interval in the injured ureteral patients. Those cases operated on 6 to 12 months after ureteral injury were, of course, much more difficult to do, and it has been our plan to operate on patients with ureteral injury as soon as the diagnosis is made if the patient's condition is satisfactory. In no instance has it been necessary to do nephrectomy after this procedure, and in no case has there been a ureteral fistula. The best results occurred in patients with ureterovaginal or ureteroabdominal fistulas following hysterectomy, and in each case the renal status improved over the preoperative status.

The second technique used was the split-tip method familiar to all, and it was used in 12 cases (fig. 4). In most of these cases ureteroneocystostomy was used in conjunction with segmental bladder resection for neoplasm. In three of these cases inferior segmental resection of the prostate and bladder neck, including trigone, was carried out because of carcinoma, after the method described by Millin. In all 12 cases a ureteral catheter or Levine tube was used for splinting and drainage and a cystostomy tube was left indwelling. All of these patients had ureteral reflux and nine of the 12 had significant postoperative pyelonephritis. In one patient nephrectomy was necessary because of renal sepsis. Intravenous pyelograms were made on all of these patients postoperatively and 2 were without hydronephrosis, 4 had 1 plus hydronephrosis, 5 had 2 plus hydronephrosis, and 1 had 3 plus hydronephrosis.

Four patients had ureterovesical anastomosis by the elliptical method described by Nesbit. A ureteral catheter or Levine tube was left indwelling in each of them and in 2 cases the patient was left on cystostomy drainage because the operation was done in conjunction with a segmental bladder resection. All of these patients had ureteral reflux and intravenous pyelograms showed 1 plus hydronephrosis in 1 patient and 2 plus hydronephrosis in 3 patients. Three of these patients have had postoperative urinary tract sepsis twice during the past 12 months.

None of the patients in this series had neurogenic bladders or previous ureteral disease on the basis of reflux.

SUMMARY

Our experiences with 28 ureteroneocystostomies have been described. A good technique of ureteroneocystostomy still remains to be discovered. The closed or pull-through technique of ureteroneocystostomy seems particularly well-adapted to the traumatized ureter following gynecological surgery.

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TRANSSYMPHYSEAL APPROACH TO THE URETHRA

JOHN E. DEES

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The simplest and most direct surgical approach to the female urethra is, of course, by way of the vagina. Occasionally a retropubic or transvesical approach to the bladder neck or first portion of the urethra may be indicated. I have recently had occasion to expose the urethra of a female child from an anterior approach after dividing the symphysis and retracting laterally the two pubic bones.

A 4½-year-old girl was first seen in October 1956 with a history of urinary incontinence since birth. There had been normal periodic voidings of good quantities of urine as a rule, but in addition there was a constant slight leakage of urine both day and night. There had been three episodes of cystitis with pyuria and slight burning on urination, but at no time had there been symptoms referable to the upper urinary tract. The history, of course, was a classical one for an accessory ureter emptying at an ectopic position in the region of the urethra or vagina. At the time of her initial examination, the urine was microscopically and chemically normal. There was no renal tenderness or mass, and the vulva on superficial examination appeared normal for a female of this age. No leakage of urine could be demonstrated during the period of inspection. Intravenous urograms showed normal appearing kidneys with no evidence of re-duplication of either renal pelvis or ureter, and the entire substance of both kidneys seemed to be adequately supplied with a single calyceal system. Cystoscopy was carried out under anesthesia, a size 16 Brown Buerger scope being introduced very easily. The bladder appeared normal throughout with one normal ureteral orifice on each side. Inspection of the urethra with a McCarthy panendoscope revealed no evidence of an ectopic ureteral orifice in this location. At this time a more careful examination revealed that what had initially been thought to be the vagina was actually the urethra which was large and patulous and easily admitted a size 28F sound. No vaginal orifice was present on the perineum or on the floor of the urethra. Bimanual rectal examination, both by myself and a consulting gynecologist, revealed no structures that could be identified as uterus or vagina. It thus became obvious that our initial impression of an ectopic ureteral opening was erroneous, and that the marked relaxation of the urethra itself was responsible for the urinary incontinence. Indeed the most difficult thing to explain was how she was able to retain urine at all.

The consulting gynecologist felt that creation of an artificial vagina was quite feasible but that this should be postponed until one of two times. If the child indeed had no uterus, and if no symptoms of retained menstrual secretions occurred at the time of puberty, creation of an artificial vagina should be postponed until immediately before marriage, so that it could be kept open by physiological means. If, at the time of puberty, symptoms or findings of retained menstrual secretions occurred, the child should be explored, and if a hidden vagina was present, it should be brought out to the perineum. If there was no vagina, a hysterectomy would be necessary.

For the following year the child practiced sphincter exercises voluntarily trying to stop the outflow of urine during individual voidings by contracting her sphincter. This produced no

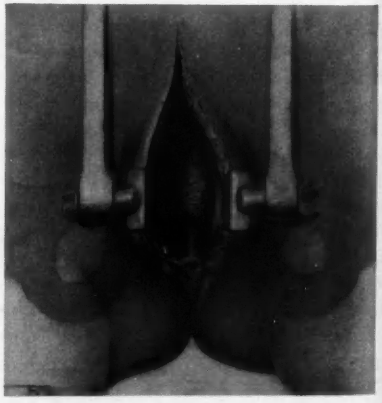

FIG. 1. Artist's sketch showing excellent exposure of female urethra and bladder neck after division of symphysis and lateral retraction of pubic bones.

FIG. 2. *A*, traumatic separation of pubic bones with separation of both sacroiliac joints. *B*, marked reduction of deformity secondary to having patient lie on his side in bed.

improvement whatsoever in her incontinence, and she was admitted for operation. I felt that a perineal approach to the urethra in this child was contraindicated for two reasons, first, and primarily, because the postoperative scarring might interfere greatly with the subsequent creation of an artificial vagina and secondly, in the absence of a vagina that surgical exposure of the urethra might be quite difficult.

On January 15, 1958, the following operative procedure was carried out:

Through a low abdominal midline incision the anterior bladder wall was exposed and the peritoneal cavity opened. A perfectly normal appearing uterus with two tubes and ovaries was present. The peritoneum was closed and the bladder opened. The vesical orifice was seen to be widely dilated and easily admitted the tip of the index finger. The abdominal incision was accordingly extended down over the symphysis pubis to the left side of the clitoris almost to the urethral orifice. The cartilaginous symphysis was divided with a scalpel without real difficulty. Using a special laminectomy retractor the pubic bones could be spread three centimeters apart which afforded a good exposure of the urethra and anterior bladder wall (fig. 1). During exposure of the urethra a small opening was made in a cavity beneath it, which apparently was a blind vagina extending up to the level of the cervix and downward to within one centimeter of the perineal floor. This opening was closed. The incision in the bladder wall was then extended downward through the bladder neck along the roof of the urethra all the way to the meatus. A portion of the redundant lateral walls of the urethra was excised with scissors and the remaining urethral mucosa, except for a narrow strip along its floor, was likewise removed. Using a continuous suture of 00-chromic catgut, the urethra was closed snugly over a size 10 rubber catheter and a second similar suture was used to plicate the tissues over the first layer and continued upward to close the anterior bladder wall around the suprapubic catheter. The pubic bones were then re-approximated by means of three interrupted sutures of steel wire which were introduced through drill holes in each bone. These sutures re-approximated the symphysis quite snugly.

FIG. 3. Patient demonstrating absence of orthopedic incapacity after resection of goodly portion of each pubic bone on each side of symphysis.

Convalescence was uneventful. The patient did not complain of pain in her back or hips, and after removal of her suprapubic tube on the

fourteenth postoperative day, she voided with a good stream without residual urine and with perfect control during the remainder of her stay in the hospital. After the patient returned home some incontinence again developed, but six weeks postoperatively control was perfect during the daytime, though some enuresis persisted.

DISCUSSION

Most of us have had occasion to divide the fibrous, intersymphyseal band in the surgical correction of epispadias with incontinence. Insofar as I am aware, this produces no aggravation of the coexisting orthopedic difficulties that these individuals characteristically have.

The orthopedists assure me that in the prepubescent child, the symphysis may be divided and separated for a considerable distance without subsequent orthopedic difficulty. In the adult, however, the pubic bones can be spread apart only a very short distance without resulting in injury to one or both sacroiliac joints. No orthopedic incapacity should be expected from resecting a portion of the pubic bones on each side of the symphysis provided that the patient has stable sacroiliac joints. Should this be done, it would be wiser not to replace the excised bone as the defect would fill in with fibrous tissue, and the chance of osteomyelitis would be reduced. Figure 2, *A* shows the x-rays of the pelvis of a man whose legs were forcibly spread apart in an automobile accident. The pubic bones were widely separated and both sacroiliac joints were likewise considerably spread. Figure 2, *B* shows considerable reduction of the deformity effected by the simple measure of having the patient lie on his side in bed.

Semans[1] has resected a portion of the pubic bone on each side of the symphysis to expose the prostate and triangular ligament in two patients with impenetrable strictures of the membranous urethra following traumatic rupture secondary to fractured pelves. He obtained good exposure of the area and there was no postoperative orthopedic difficulty (fig. 3). Although rarely carried out in this country today, obstetricians for many years divided the symphysis with a gigli saw in cases of contracted pelves to facilitate delivery. These women usually experienced no subsequent orthopedic difficulty secondary to this procedure, but on occasion, osteomyelitis or sacroiliac pain did develop.

This single case is not being reported for the purpose of advocating transsymphyseal or transpubic exposure of the urethra as a routine or frequently used procedure. In certain highly selected cases, however, this approach may be indicated and may be expected to afford good exposure of the bladder neck and urethra in the female and of the prostatic urethra and region of the triangular ligament in the male.

[1] Semans, J. H.: Personal communication

DISCUSSION

DR. REED M. NESBIT (Ann Arbor, Mich.): I want to discuss Dr. O'Conor's wonderful movie.

The first Marshall-Marchetti operation that I ever performed was in a woman who had had two operations accomplished from below by very competent gynecologists. The first time I saw her she had already had one of these operations, and I referred her to our professor of gynecology. She said, "I don't want to go to him. I have come to you." I said, "He has had so much experience with this condition that he should take care of you."

I saw her six months later and she was totally incontinent. She said, "I will never be satisfied until you have operated on me"; so I operated on her.

I was going to perform a sling operation, which I think is unphysiological because it provides some degree of obstruction, not physiological continence. When I operated upon her, to my utter horror, I could not even find her urethra, so successful had been her two previous operations and I could not get around the urethra either, so I thought I would try to do something of the nature that Marshall and Marchetti have described.

This woman simply had a cystopexy with silk, and she was totally and completely continent after the operation and has been so for seven years.

My associate, Dr. Jack Lapides, is going to present a paper at the American Urological Association meeting next week* which I hope all of you will hear because I believe it is one of the landmarks in our understanding of the control of urine. He has found that when he shortens the urethra by excising pieces of the urethra from animals, the critical length of the urethra for continence in female dogs is 2 cm. Shorter than this length of urethra in dogs will give rise to varying amounts of incontinence.

One of the things he has found, which perhaps has a bearing on this matter under discussion, is that when he has cut the urethra off so that it is barely continent, so there is a little bit of outflow, if he puts stay sutures at the end of the urethra and lengthens the urethra by tension, the bladder no longer is incontinent. So, lengthening of the urethra and putting it on tension under those circumstances appears to be a factor in gaining control.

It is his belief and mine also that the success of the Marshall-Marchetti operation isn't due to the changing of the angle of the urethra or anything of that nature, but rather lengthening the urethra and fixing the urethra in an elongated fashion so that it will have greater tension upon it.

There was an operation designed by a man by the name of Dudley in 1905 which was his presidential address at the American Gynecological Society, and published in their transactions in 1905, in which he said that most women who have stress incontinence have a urethral meatus that is quite a long way off from the clitoris, and he simply moved the urethra up to a position close to the clitoris and said he cured many cases.

I heard about this at a panel discussion on stress incontinence at Atlantic City, at the American College of Surgeons meeting last fall, and I asked Dr. O'Conor to find out if they are still doing this operation in Chicago. He found out that they are, and that the procedure is still successful. So, in that case they are lengthening the urethra and fixing it at the other end.

I would suggest that if we have failures, which we may have occasionally with the Marshall-Marchetti operation, we go to the Dudley operation and lengthen and fix the urethral meatus at the other end.

I have come to the place where I don't care if I put any sutures in the urethra at all. I never put any in the vagina. The only thing I am concerned about is picking up the lower segment of the bladder at its outlet and putting two rows of silk sutures to the periosteum and to the posterior rectus sheath.

DR. CHARLES A. W. UHLE (Philadelphia, Pa.): I enjoyed Dr. O'Conor's motion picture very much indeed. I have been interested in this problem for a number of years. To date we have 26 cases that we have operated upon in Philadelphia with an 88 per cent cure rate. In two of the three patients who were unsuccessful the choice of case was very poor on our part. As Dr. O'Conor stated, you have to be very careful in your selection of the patient.

The third patient, who obtained no result after one year, did have a good result immediately

* J. Urol., **80**: 341–353, 1958.

after the operation, which lasted for about a year. She had a chronic cough during this time. At the end of a year severe viral pneumonia developed, and very severe cough; following the pneumonia she became incontinent again. In this particular patient the exact technique, which I will show you, was not followed. Sutures were placed on either side of the urethra and only one or two in the bladder region, tacking the bladder to the rectus wall.

I go along with Dr. O'Conor's feelings that the important sutures are on either side of the urethra at the vesical neck and one on top of the vesical neck, but I also feel that some of these cases break down because those sutures fail to hold. Therefore, to protect those sutures from the strains of intra-abdominal pressure I have been tacking the bladder wall to the posterior rectus wall, as I will show you on the diagram. One of our patients is a very severe asthmatic. She has been perfectly well for about three years following the suspension operation. I do feel that these bladder wall sutures are protection to the important sutures at the vesical neck and at the urethrovesical junction.

[Slide] Dr. O'Conor has stated that many of these patients have had previous gynecologic surgery. Here is one patient who was referred to me some five or six years ago. She had undergone anteroposterior colporrhaphy for stress incontinence. The result was unsatisfactory. She did not want the Marshall-Marchetti procedure performed; she said she was too old. Therefore, a Foley catheter was inserted into the vagina. She wore this balloon catheter for three years with absolutely perfect continence. She was the happiest person, and stated that for the first time in several years, she was able to keep her powder dry. (Laughter)

This would tend to agree with Jeffcoate's idea and Marshall-Marchetti's idea of elevating or restoring the urethrovesical angle in this particular idea rather than lengthening the urethra, as Dr. Nesbit just stated.

This technique is one that be used in elderly patients and is successful only if the introitus is tight. If the introitus is not tight, the balloon catheters will be forced out. This is a very satisfactory way of handling some of these problem cases.

[Slide] This shows the placement of the sutures in the periurethral and bladder areas. One zero chromic suture material is used. It also demonstrates the areas on the symphysis and posterior rectus muscle wall where the structures are suspended. Note that a double bite is taken with the suture in the perivaginal tissue. And by all means stay away from the urethra.

[Slide] This shows diagrammatically what happens. The urethra and vesical neck are pulled up to the posterior aspect of the symphysis, and you can see the accentuation of the urethrovesical fold in that area, which some investigators believe is necessary to restore in order to have a perfect result.

We have had no complications except for two cases of foot drop. I believe that this was due to the fact that the patient's legs were separated and slightly flexed. The intern who had his finger in the vagina to elevate it probably was resting upon the patient's leg, and there was also a strap over the ankle region. This may have had some bearing on the foot drop. I mention it because it is a very annoying complication.

About a month or two ago a nurse, who had been incontinent ever since she had undergone a Marshall-Marchetti operation, was referred to me. I mention this purely for your interest. If you operate upon these patients who have had a previous operation, it is quite a job to dissect free the bladder and urethra in the retropubic area. In this particular case I had to leave the urethra and the vesical neck attached to the pubis, and work down into the lateral recesses. When I got down to the vaginal floor, or what I thought was the vaginal floor approximating the vesical neck, I put a double-whip suture in, as you saw in the previous slide, 0 chromic, and brought the vaginal tissues up to the symphysis pubis. I also suspended her bladder to the posterior rectus wall.

This patient had a perfect result. I got into the bladder three times. I mention this to you as a very difficult procedure because there are so many adhesions. When you re-enter the retropubic area after another operator has preceded you, you will not have a very easy time. So be prepared to accept the difficulties.

My compliments to Dr. O'Conor for an excellent movie.

DR. GERSHOM J. THOMPSON (Rochester, Minn.): I want to arise to emphasize a point in Dr. Dees' presentation.

[Slide] Some time ago we saw a young man who had osteomyelitis of his pubic bone. From time to

time he had multiple perineal fistulas and sinuses, and finally a large fistula from erosion of the urethra. This bone condition came on metastatic after he had a furuncle at the age of 16.

[Slide] This shows the way the pubis was resected. The preoperative film is here, and this is the postoperative film showing partial resection of the pubic bone.

[Slide] This shows the appearance five years later. Meanwhile multiple sinuses had developed again, and urethral leakage.

[Slide] This slide shows the appearance some eight months after complete resection of the pubis. Note that his sacroiliac joints are in rather good condition.

[Slide] This shows the appearance some four years after the last operation. He had absolutely perfect anatomical function. He walked in a perfectly normal way. This shows how widely these pubic bones can be resected and still have a good anatomical function.

I think one need not worry, if you are doing this procedure of Dr. Dees', about instability of the pelvis. I am not certain that even wiring is necessary. Perhaps just a pelvic sling for a week or ten days postoperatively is enough.

Dr. Grayson Carroll (St. Louis, Mo.): I would like to make a comment about the Marshall-Marchetti operation. We have been doing it and find it very successful.

In selection of the case it is an advantage if you fill the bladder and then have the patient stand. Place the finger in the vagina and press gently over the urethra and have the patient cough. If no urine is expelled by that measure you can rely pretty well on the possibility that the operation will be successful.

In using this procedure I have been amazed to discover how much of the female urethra can be exposed by the retropubic route. Looking at Dr. Dees' procedure, in which he separated the symphysis, I am quite sure it was necessary in that instance, but it is amazing how we can expose the entire length of the female urethra by this retropubic exposure.

We use chromic catgut, not silk. We also have abandoned the idea of tacking up the urethra; rather, we put some stitches in the vagina laterally and also at the bladder neck. I also believe that tacking up the bladder, bringing the sutures through the rectus muscle, is rather an important procedure. We have had success in all of our cases, and recommend it to all urologists.

Dr. Austin I. Dodson (Richmond, Va.): I wish to say a word or two about Dr. Valk's presentation. The first review of the literature and discussion of ureteroneocystostomy was done by Dr. Bovee in 1900. At that time he reported that 80 operations had been done by 60 surgeons, with excellent results. At that time careful followup studies of those patients were not made, and I suppose this accounts for the fact that the results then seemed to have been better than we have had since.

It is interesting to note that there have been three major needs for reimplantation of the ureter, the first at the time that Bovee reported; practically all ureters were transplanted because of injury. They were dealing with smaller ureters perhaps than the latter cases.

The second period of reporting, when a number of papers appeared in the literature, was in the late 1920s. The major cause for reimplantation followed segmental resection of the bladder. Beer followed twelve of his patients for a long period of time with followup pyelograms and found that immediately eight of those patients had excellent results. After a period of five years only five had excellent results.

In most recent years ureters have also been reimplanted because of reflux from the bladder.

Most surgeons have emphasized the fact that failures always followed too much tension on the ureter and an insufficient amount of the ureter projecting within the bladder. In some instances, the ureter had retracted back into the bladder wall, and in other cases there had been constriction.

Kelly emphasized the importance of mobilizing the bladder and fixing it high into the pelvis to take the tension off the end of the ureter. I called attention to the fact some years ago that the ureter could be straightened, liberated, and considerable length added to it by straightening the ureter through the true pelvis without interfering with the blood supply, provided care was taken not to strip off the tissues immediately surrounding it.

Dr. Valk's paper has indicated that in most instances and in most types of operations very good results can be obtained if the cardinal principles of plastic surgery, such as absolute immobilization, absolute freedom from tension,

and preservation of the blood supply are taken care of.

DR. MEREDITH CAMPBELL (Miami, Fla.): Dr. Goodwin brought my name into this. I would be interested, as a matter of personal information, to know how many in the audience have used jejunum as a replacement in deficit ureteral surgery.

I had occasion during the past year to do a ureteral replacement in a 14-year-old boy who had a deficit of about 15 cm. He was on nephrostomy drainage. We could not figure why, physiologically, jejunum should not be used. It is a little smaller gut than ileum. We took a piece about 5 feet down from duodenum and it worked beautifully. It made a smaller conduit than does ileum, but the striking thing was that only about 25 per cent as much mucus and sludge were obtained from the jejunal segment as compared with the lower ileal bowel. That makes quite a difference in the appearance of the urine.

I was interested in Dr. Dees' presentation because in attacking the urethra in the female, and particularly epispadias, I always divide the symphysis. I have even had occasion to divide the solid symphysis in three patients, two of whom were males. The only difference in the re-suture is that you have to drill holes to put in the steel wire sutures.

DR. JOHN HAND (Portland, Ore.): I would like to comment on Dr. Dees' interesting references to the symphysis pubis.

In Oregon and Washington men working in the forests frequently sustain severe injuries involving fractures of the pelvis. These are often accompanied by displacement of the symphysis pubis and rupture of the urethra. When the urologic complications of these injuries are managed without correcting the displacement of the symphysis, tortuosity of the urethra follows and the strictured areas become difficult to keep dilated.

Consequently, in such injury, I realign the symphysis and wire it at the time I care for the extravasation and do the preliminary cystostomy. This realignment of the symphysis swings the cut urethra into proper position. Thus, as healing occurs, the possibility of urethral tortuosity is minimized and strictures are easier to manage.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): May I ask a question? According to Dr. Valk's figures, the Dodson method has a 7 per cent incidence of reflux, the split-tip method 33 per cent, and the Nesbit method 100 per cent.

Has Dr. Valk or Dr. Dodson cystoscoped these patients to see whether there a nipple is formed which might account for this difference?

DR. WILLARD GOODWIN (Los Angeles, Cal.): In my closing remarks I would like to show one or two more slides.

[Slide] This slide shows the ileum three and a half years after it has been part of the urinary tract. You can see that it is normal.

DR. CARROLL: Do you get a lot of sludge?

DR. GOODWIN: All of the patients have mucus, but it has not been a problem with them, although it may be in some ileal bladders.

This is a patient who had a bladder flap operation on the left side and the ileal ureter on the right. I believe you can see that the right kidney is as good as or better than the left, and it now turns out clinically that the left kidney is going bad.

[Slide] This shows the patient who had uremia due to poor renal function and on whom we had later to do a Bricker operation. You can see that the nonprotein nitrogen rise and the acidosis were very severe. When the ileovesical channel was interrupted, the figures returned to a more normal level. Don't do this operation on a patient with poor renal function.

[Slide] This is a child similar to the one Dr. Campbell mentioned, with a nonfunctioning right renal shell and loss of the upper portion of the ureter. This is an extraperitoneal ileal ureter (most of them have been intraperitoneal). He passed the calculi that were lodged in the lower calyx, and he is now free of calculi.

[Slide] This patient had to return to surgery because of a leak at this point. A T-tube was put in, giving a chance—

[Slide] —for this. (Combined cystometrogram and nephrometrogram.) This is the bladder and the kidney pressure. You can see that the pressure does rise in the kidney, as it does in the bladder, although the loop does seem to protect the kidneys.

[Slide] These are the various types of ileal ureters that have been used. I should like to emphasize that I think they should always be isoperistaltic and that it is a mistake to use an ileal loop that is antiperistaltic.

[Slide] This is simply a demonstration of technique which emphasizes that the isolated

ileal segment should be taken a long distance from the ileocecal valve in order to allow the segment to drop down to the back of the bladder. The anastomosis should be made if possible on the fixed part of the trigone on the back of the bladder far down, and a window should be cut out of the bladder.

Dr. William L. Valk (Kansas City, Kans.): Five years ago, when we decided to use these three methods alternately for ureteroneocystostomy, we considered the use of the various types of nipples, intussusceptions, and cuffs that have been advocated. We felt, however, that since in a closed system pressure is exerted equally in all directions, these techniques were not sound from a hydraulic standpoint.

When we look into these bladders we are glad to see a ureteral orifice which is flush with the bladder wall, because to us it looks like a normal ureter. If we watch it long enough, we will see that ureter open and close with peristalsis.

Whenever mucosa-to-mucosa anastomosis is done and you look into the bladder, you see that the end of the ureter is kept open by its anastomosis to the bladder mucosa. In the elliptical anastomosis it of course approximates almost a diverticulum.

We believe that the reason urine normally does not reflux from the bladder in the absence of unusual peripheral resistance or obstruction is because of the innate ability of the ureter to remain in systole at that point, and that it probably is unphysiologic to open the ureter then and suture it abnormally to the mucosa.

I wish to thank Dr. Dodson for his comments. His method of closed ureteroneocystostomy is certainly a very excellent technique, as our followup studies seem to indicate.

Dr. Vincent J. O'Conor (Chicago, Ill.): I am glad that Dr. Carroll brought up the important point of the so-called Marshall test. This test consists in filling the patient's bladder with about 300 cc water, having the patient then strain to urinate, and, thus, increase the intra-abdominal pressure. If the sphincter is incompetent when the patient coughs, there will be a jet of urine coming from the urethra without her control. Marshall originally injected a wheal of novocaine in the anterior vaginal wall at the area of the junction of the urethra and bladder neck, and took hold of the mucosa with an Allis clamp, pushing upward and backward on this area, and having the patient strain and cough at the same time. If, after this maneuver, there was no jet or loss of urine from the urethra, he considered that the patient was a good subject for retropubic urethropexy and cystopexy.

We have found that it is not necessary to do this procedure in this manner. Our method is to fill the patient's bladder with 300 cc sterile water with the patient in the lithotomy position on the table. A small wad of gauze or cotton is placed upon the end of a Kocher clamp or similar instrument and pressure is then exerted upward and backward at the urethrovesical junction. The patient then raises up on her elbows, strains and coughs. If there is no loss of urine, we consider this to be evidence that the patient should benefit by a urethropexy.

COMPLICATIONS AND UNFAVORABLE RESULTS FOLLOWING OPERATIONS FOR URINARY DIVERSION

PRESIDENT CAHILL: We have this subject on the program for a panel discussion. The moderator is Dr. Reed M. Nesbit. The participants alphabetically are Dr. Justin J. Cordonnier, Dr. Charles C. Higgins and Dr. Harry M. Spence.

CHAIRMAN NESBIT: A few months ago at a meeting, during the breakfast hour, some people were sitting at a table and began talking about the vicissitudes of supravesical diversion when the ureter is severed from the bladder and is moved to some other site. There were a good many of these things discussed at that particular moment. Your Secretary overheard some of the comments, and said he thought it would be a good subject for discussion for the present meeting. That is the reason why this panel discussion is being held.

It was his hope (and it is the hope of the people sitting at this table) that each and every member in the Association will participate in this discussion if they have discussion to introduce, and if any in the audience wish to direct any questions to any of those sitting at this table, please feel free to do so. Or, if any in the audience would like to address a question to someone else in the audience regarding the matters under discussion, please feel free to do so. If you will raise your hand at any time during the discussion, we will recognize you and welcome any remarks you may wish to make.

The discussion will be confined to supravesical diversion in which the ureter is separated from the bladder and brought to some other site than the bladder.

Starting off with cutaneous ureterostomy, Dr. Cordonnier has some remarks to make about this procedure.

DR. JUSTIN J. CORDONNIER (St. Louis, Mo.): I feel that this particular procedure, expressed to this group before, has a lot of hidden difficulties that perhaps are not emphasized enough. It is very difficult to find a series of cutaneous ureterostomies discussed, and the only two ones I know of are those of Abeshouse and those of Whitmore and Marshall.

An analysis of these series will show that the morbidity in cutaneous ureterostomy is higher than that of ureterosigmoidostomy. I think too much emphasis has been placed on the idea that the principal objection is that collection of the urine is mechanically difficult. A lot of people have given their ideas about technique, but very few have presented followup data.

We have tried to follow these patients who have had both ureterosigmoidostomies and loop diversions to see whether they are doing well or poorly, and I think if one subjects cutaneous ureterostomy to the same analysis, he will find that most of those are doing poorly.

DR. HARRY M. SPENCE (Dallas, Texas): In general, I will go along with that. I know that to talk for cutaneous ureterostomy in 1958 is like wearing high-button shoes when everyone desires the "chemise look." I gave up cutaneous ureterostomy because I thought it was substituting one disease for another.

A few years ago, however, the idea was brought out of making a nipple to which a condom could be attached to do away with the indwelling catheter. I revived a little interest in it then, and I would like to show a slide of my best results.

[Slide] I believe Dr. Fish brought out this technique. It is a two-stage procedure. The first operation consists of turning down a flap of skin and making a snout, and at a second operation tunneling through it with the ureter.

Here the patient is lying flat. This is the navel. We had only one kidney to deal with. Here is the snout that we made. [Slide] Here is the collecting device which does away with the inlying catheter. We found that although this looked very good, we still had trouble with stenosis of the stoma, and we found that if we put the elastoplast or tape around the snout tightly enough to keep the urine from leaking, we tended to get a fistula on the undersurface; so, I don't believe that is the answer.

I do not think we ought to give up completely the cutaneous ureterostomy, however, and while we are not talking here about indications, I think the secret of avoiding complications is to use it in the right case. In my opinion the right case is a single ureter to be diverted, a big ureter that has a good blood supply, and I think the way to do the operation is to bring the ureter out through a stab wound and leave a little rosebud.

DR. CHARLES C. HIGGINS (Cleveland, Ohio): In what percentage of patients on whom you would use that technique would stenosis develop?

DR. SPENCE: The pull-through? I am sure an appreciable percentage would, but if you use it on a big ureter I think you will come out all right.

DR. HIGGINS: I believe that stenosis can usually be avoided by using an intussusception technique in performing a cutaneous ureterostomy. The mucosa of the ureter is gripped while the free end is pulled back, thus causing an intussusception for approximately from 1½ to 2 inches. The turned-over, everted end of the ureter is sutured in position with three or four fine silk sutures, so that a permanently everted ureterostomy is constructed, thus the mucosa of the ureter protrudes on the abdominal wall.

DR. JOHN A. TAYLOR (New York, N. Y.): Before the panel leaves the subject of ureterostomy, I have had cases in which, after Wertheim and similar procedures, I was forced to do a ureterostomy through the back. I have been surprised at how well the patients have got along. I wonder if you men have had much experience with that.

CHAIRMAN NESBIT: Did they require intubation?

DR. TAYLOR: Yes.

CHAIRMAN NESBIT: Does anyone in this room have any technique in cutaneous ureterostomy that will consistently avoid stenosis?

DR. NORRIS J. HECKEL (Chicago, Ill.): I feel that there is a very definite place for cutaneous ureterostomy. The first one I did was in 1936 and the patient is still living and well. His pyelograms are normal.

I feel there is a way to do this operation so that the patient does not have to wear catheters. We make a trough out of the skin and then make a rosebud from the cut end of the ureter. We then suture the ureter to the top of the trough. Of course, you will have complications, but in our experience the complications are not due to the technique of the operation but to the postoperative care that the patient receives.

DR. JOHN K. LATTIMER (New York, N. Y.): I would like to say, in regard to the reference to Dr. Whitmore's work, that he recently presented a comparison of several methods of urinary diversion at a meeting in New York. While he did say that his cutaneous ureterostomy cases had a surprising number of complications, nevertheless they were not quite so frequent as the ureterosigmoidostomy complications. However, his series did not include a large proportion of patients who required no inlying catheter in their cutaneous ureterostomy.

In other words, we don't have too much information from Dr. Whitmore's series about how well patients might do if they did not have to have a permanent indwelling catheter.

In reference to the idea of keeping the end of the ureter open, my own practice with our tuberculosis cases is to provide the patient with a bougie and have him pass it into the ureter each week himself, in order to keep it open. It works surprisingly well.

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): I should like to corroborate what John Taylor has said about letting the patient dilate his or her own ureterostomy. They can and do, and when that is done I don't believe that stricture will be a problem.

The major technical feature is seeing that a piece of fascia is removed from the abdominal wall along with some muscle so that the ureter will not be strictured in this part of its course.

The problem of accommodating to collecting devices is individual. Marshall, Whitmore and Hudson produced a motion picture for the American Cancer Society showing a patient going in swimming with Singer cups.

With proper technical management cutaneous ureterostomy is associated with fewer complications than other plans of diversion.

DR. ARCHIE L. DEAN (New York, N. Y.): I agree that cutaneous implantation of the ureters is the worst way to accomplish urine diversion, but I think we should realize that this method is used almost exclusively on patients seriously ill with infected kidneys and dilated ureters.

Other parts of the transplanted ureter can become stenosed besides the skin junction. As one follows changes in the course of the ureter from the kidney pelvis to the skin one observes four or five different planes through which the ureter must pass. At any of a number of bends the ureter may be partially occluded by pressure of fascia or muscle.

Another thing that has been emphasized already is the importance of aftercare. Patients on whom I have done this operation, who live nearby and whom I can observe and treat, do very much better than those patients who live

at a distance, and whom I return to their local physician or urologist. It is difficult to arouse the interest of someone else in your operation, and these patients require close observation and prompt treatment when they need it.

DR. RAUL LOPEZ ENGELKING (Mexico, D. F.): I agree with Dr. Spence that one of the few indications of cutaneous ureterostomy is a solitary kidney. We do it as palliation in those cases of pelvic invasion of carcinoma of the cervix.

We should not accomplish major surgery.

CHAIRMAN NESBIT: Do you mean with a dilated ureter?

DR. ENGELKING: Yes.

DR. JOHN K. LATTIMER (New York, N. Y.): In regard to the matter of putting skin flaps of any kind around the ureter, I can quote the experience of Drs. Fish and Hudson of our Cancer Unit as well as our own experience, wherein any time we have used a full thickness skin flap and tried to apply it to the ureter we might get a very beautiful result for a short period, but as time goes on not only did the skin flap begin to retract to some degree, but also the subcutaneous fat began to atrophy and we were left with a flaccid, completely unsatisfactory bud, which was of no use in attaching any cup or device. We have abandoned the idea of putting skin tubes around ureteral buds. We do apply pinch grafts or split thickness grafts to some protruding ureteral buds, to toughen them up, however.

DR. HOWARD I. SUBY (Boston, Mass.): I would like to have this panel give me an answer as to what percentage of patients who start out with skin ureterostomy eventually have to be intubated.

CHAIRMAN NESBIT: Dr. Suby asks the panel to discuss this question: What proportion of patients who start out with a cutaneous ureterostomy end up with an intubation of it?

DR. SPENCE: I have three patients with cutaneous ureterostomy currently alive, and all of them are wearing tubes.

DR. HIGGINS: In instances in which the intussusception technique is employed, intubation is not necessary.

CHAIRMAN NESBIT: You are stating a paradox, Charlie. You say all of yours are intubated?

DR. HIGGINS: Not at all, intubation was deemed advisable in the patients in whom I performed cutaneous ureterostomies prior to employing the intussusception technique. With this procedure I have found intubation is not essential.

DR. CORDONNIER: We have only done four or five, because I have never been sold on the procedure. About 50 per cent have required intubation. Those who are not intubated have come in very frequently to have their stoma dilated.

CHAIRMAN NESBIT: Every one I have seen in our own institution who started out with a cutaneous ureterostomy ended up with a tube, except two cases in which plastic surgery was performed and a Z-plasty was utilized to correct the stenosis.

Now, based on that experience, and with the advice of some plastic surgeons, we are starting out with the insertion of a piece of skin into the stoma, hoping to avoid it.

[Demonstration on blackboard.]

If we start out with a skin flap like this, and leave a flap of skin to be inserted into an incision in the ureter, it is hoped that by this technique, which has been successful in correcting some of the stenoses, it might be avoided in the future.

DR. JOHN F. PATTON (Washington, D. C.): I would like to say something in favor of skin ureterostomy. If I could always be assured of obtaining a nice stoma, similar to a miniature colostomy, and eliminating the need for catheters, I would prefer this method in most cases. I have one patient who has lived happily for 12 years with a skin ureterostomy, wearing a Rutzen bag. We made a circular incision in the fascia and a circular incision in the skin, allowing the ureter to protrude about 2 cm. A catheter was left in place during the first few postoperative days and the ureter rolled back into a nice rosette. She has not worn a catheter since, has never had an episode of pyelonephritis and there has been no necessity for dilation of the stoma.

If a technique could be devised to insure a similar result in all cases, skin ureterostomy has much to offer.

CHAIRMAN NESBIT: We will go on now to ureterocolonic anastomosis. This will refer to ureterosigmoid, ureterorectal and such types of anastomoses.

Dr. Higgins, will you start the discussion?

DR. HIGGINS: My remarks will be rather brief. I am substituting for Dr. C. D. Creevey this morning. At the last moment he could not participate on this panel. I am discussing this same subject at the meeting of the American

Urological Association in New Orleans* and desire to avoid reiteration.

Apparently I am one of the unfortunate surgeons who, over a period of years, has found that the Art of Surgery is not always a bed of roses. I do have operative mortalities, George, and I believe I have encountered practically every complication that may succeed ureterointestinal anastomosis.

In my experience, ureteral obstruction is the paramount issue. I have observed leakage from the site of anastomosis in two instances. In one instance, urine drained into the abdominal cavity; and in the other, into the abdominal cavity and the left thorax. Nephrostomy was performed in each patient, and later the ureter was reimplanted into the rectosigmoid. In one child, cardiac arrest occurred during the nephrostomy, but cardiac massage brought about recovery. Acute pyelonephritis immediately after ureterointestinal anastomosis is at the present time unusual.

Obstruction following implantation of the ureter into the bowel may come about as follows. Many surgeons still employ the Coffey I or II procedure, wherein a portion of the ureter protrudes into the lumen of the bowel. On about the fifth postoperative day in many instances this protruding portion of the ureter sloughs off, but in other instances it may be retained. Through the proctoscope the retained knob looks like a cherry, and with subsequent inflammation and edema produces a definite obstruction to the passage of urine into the bowel. I have also observed ureteral obstruction due to stenosis after use of the mucosa-to-mucosa technique of implanting the ureter into the bowel. I have observed obstruction of the ureter where it rests in the trough in the bowel wall, and where the ureter enters the trough in the bowel wall. I have observed a hydroureter following ureterointestinal anastomosis, in which exploratory operation failed to reveal ureteral obstruction. Whether or not in such a case the difference in intraureteral and intracolonic pressure plays a role, I do not know. We are aware that intracolonic pressure is about 270 cc water, and that intraureteral pressure is approximately 33 cc water. This difference in pressure may be a more important factor than might be presumed. In the large majority of instances, after ureteral obstruction, there ensue delayed complications such as stasis, hydronephrosis, pyelonephritis, and impairment of renal function. Hyperchloremic acidosis may be a problem of considerable magnitude, which I believe occurs whether the kidneys are abnormal or normal. In most of the patients I have observed with hyperchloremic acidosis following ureterointestinal anastomosis the kidneys were not normal. I prefer to treat patients with hyperchloremic acidosis with 10 per cent sodium citrate solution (given orally); the dosage is correlated with the findings from blood studies.

DR. SPENCE: I would say a little bit about reflux, and show a couple more slides, but I believe the projector has been changed, so I won't show them.

I think reflux is getting to be sort of a naughty word, but I am not sure that it is quite so bad as we have been led to think. I was going to show you a case of transplant (admittedly ill-advised) in exstrophy to the sigmoid, ill-advisedly with my retrospectroscope, Dr. Chute, in which this child had reflux of air in every film taken for a period of ten years. She started off with very badly damaged kidneys, and she ended up dead, but during this 10-year period she was hospitalized only a couple of times and led a surprisingly normal life.

The reflux from that one case and from a few others I don't believe is quite so bad a prognostic sign as we have been led to think. The question arises in my mind as to whether, if you have reflux in a patient who is doing well clinically, you should change over to an ileal segment or something else. I believe we will discuss that later. That is my first point.

The other point is that I think there is a difference in the complications that follow transplant to the intact sigmoid in infants and children for exstrophy, and in adults. I don't know why that is. My theory is that the infants evacuate their bowels so frequently that they don't have time to get a lot of absorption. For exstrophy in infants I think it (conventional ureterosigmoidostomy) is still all right, despite the fact that we are going to have some delayed complications. I think when such complications occur we ought not wait too long to bail them out. That has been my failing.

Concerning ureterosigmoidostomy complica-

* J. Urol., **80**: 279–292, 1958.

tions, I have had three cases that formed stones in the ureter—not in the kidney but in the ureter. On each one of them we have done ureterolithotomy and have found in each case stenosis at the site of the anastomosis, which we corrected, and currently they are doing all right.

DR. HINMAN, JR.: May I ask Dr. Spence if he uses any cotton in his anastomosis, or does he use silk?

DR. SPENCE: I use Justin's end-to-side technique, and the outer layer of sutures is fine arterial silk. For the mucosa-to-mucosa layer I use fine catgut.

DR. HINMAN, JR.: Would that be a factor in the appearance of stones?

DR. SPENCE: The stones were all above that, Frank. I will think about it.

DR. HIGGINS: Did the patients in whom you noticed the reflux have direct anastomoses or was the trough principle used for them?

CHAIRMAN NESBIT: Virtually all of the direct anastomoses without the tunnel show reflux, in my experience. It is too bad that Dr. Henry M. Weyrauch and Dr. Wyland F. Leadbetter are not here, because it would have added a great deal to our discussion if either or both of them could have discussed the combined technique of direct anastomosis with the tunnel.

Are there any persons in the room who have had considerable experience with that type of technique and who would like to discuss it?

DR. RICHARD CHUTE (Brookline, Mass.): I have used what we in the East call the Leadbetter technique, and what west of the Mississippi you call the Weyrauch technique, in quite a series of cases in our hospital, and I have had what I consider really excellent results. There have been very few cases of stenosis and dilatation of the ureter above—and I can think of no cases of reflux. I think it is a very valuable technique.

CHAIRMAN NESBIT: In regard to reflux, I would like to point out a little trick in technique that we discovered a few years ago in studying some of our patients.

Reflux can sometimes be demonstrated by a urokon enema, but we found in more than one case that a delayed urokon enema would reveal reflux when an immediate one did not. That is a point to think about if you are investigating any cases for reflux by roentgenology.

Dr. Cahill, I would like to ask you what your present feeling is about ureterosigmoid anastomosis. I know you were doing a great deal of these at one time. What is your present feeling?

PRESIDENT CAHILL: I would think our complications and your good results probably parallel those of everybody else. The paradox is that you operate upon these people; you make a tunnel; you can do a mucosa-to-mucosa transplant, you can drop the thing back and close the patient up, and about one-third of the patients will have perfect results. You do the same thing on two-thirds of them, and then you start to find obstruction. You begin getting infections, which may not show sometimes for from one to three years.

Another paradox is that you will have obstruction that will last a year, then sometimes will disappear.

The question asked is what we did when we got the good results that we might not have done when we got poor results. I have two cases now that Dr. Higgins did some twenty-odd years ago. One is a rabbi in New York City. He has an old-fashioned Coffey, perfect kidneys, perfect ureters, perfect control by rectum, no acidosis at any time. That was one of Dr. Higgins's earliest cases.

We have had the same things ourselves, and yet at the same time, with the same technique, we have had bad results. What is happening? It must be that the blood supply is impaired, or infection occurs, or thrombosis and necrosis occur to change the whole picture.

DR. SPENCE: Dr. Cahill, do you think I am right or am I kidding myself that there is a difference in doing it for exstrophy and ovarian cancer?

PRESIDENT CAHILL: I had several carcinoma patients in whom I did not take out the ureter high enough, and they had necrosis at the terminal end of the ureter because I shut off the blood supply. Every time after that I made sure that the end of the ureter bled. If it didn't bleed I cut some off. I cut some off until it bled.

It is very simple to make sure you have a blood supply, to establish the fact that it is not all coming up from below rather than down from above. I try not to strip out the ureter. Leave as much of the tissue as you can, because in that tissue is the blood supply.

I think you damage the blood supply just

like you damage the blood supply in cutaneous ureterostomies. You must bring them out and everything with them. Strip them out, and then you take out the tube in a week and out comes four inches of ureter with the tube necrotic. In other words, what you do is the thing that determines it. It isn't that cutaneous ureterostomy is good or bad. It is either the good methods you use or the lousy methods.

DR. HIGGINS: Frequently in the presence of carcinoma of the bladder, one or both ureters may be thickened. In my experience, the results secured in this group of patients are not so satisfactory as in individuals in whom the ureters are normal at the time of ureterointestinal anastomosis.

CHAIRMAN NESBIT: Dr. Willard E. Goodwin, will you report to us on your two techniques of ureterointestinal anastomosis—first the one you described along with Hudson, in dealing with exstrophy cases; and second the open procedure for ureterorectal or sigmoidal anastomosis in adults? Will you report about those to us?

DR. WILLARD E. GOODWIN (Los Angeles, Cal.): The first technique we reported was the Maydl-Bergenhem procedure of transplanting the trigone for exstrophy. Dr. Hudson and I did that in three or four patients, and we have not done it since then.

CHAIRMAN NESBIT: Why not?

DR. GOODWIN: We have rarely had an opportunity since then, and now I believe there are better ways of doing it.

PRESIDENT CAHILL: I might say that Dr. Lattimer might report on a higher series than that. How many do you have (by the Maydl-Bergenhem technique)?

DR. LATTIMER: Nine.

PRESIDENT CAHILL: Only two of them were any good.

DR. GOODWIN: I have not had the opportunity to follow those patients personally. I think Dr. Scott has done a Bricker diversion on a couple of them, and in one a stone developed. That was not the answer.

Since we learned to do the technique of ureterosigmoidostomy through the open bowel, we haven't had trouble with stenosis. This is a technique which is the same as the Leadbetter or Weyrauch, except that it is done from inside the bowel instead of outside. It brings the ureter in posteriorly, where it lies anyway, and mobilizes a very small segment of the ureter. It does not destroy its blood supply, and the results are uniformly good as far as technique goes. A submucosal tunnel is formed.

We don't have stenosis or sloughing or leaking, yet some of these patients have reflux. I can't tell you how many do, but some do and others don't. We have never done it any other way since we learned to do it this way. I suppose that series is perhaps twenty or more patients now.

CHAIRMAN NESBIT: Are you still advocating and practicing that procedure?

DR. GOODWIN: Yes, sir.

DR. CORDONNIER: What percentage of your cases of carcinoma of the bladder did you do a ureterosigmoidostomy on?

DR. GOODWIN: Personally, I prefer the ureterosigmoidostomy by that technique. In our institution, however, where other people are doing operations too, the residents particularly like to do the Bricker operation. I suppose it is about 50:50 or perhaps higher than that—perhaps 60 per cent Bricker's and 40 per cent ureterosigmoidostomies.

DR. CORDONNIER: By our technique?

DR. GOODWIN: Yes. It is not done by any other technique in our institution.

CHAIRMAN NESBIT: Dr. Archie Dean, a few years ago you talked about using this particular technique. What has been your experience?

DR. ARCHIE L. DEAN (New York, N. Y.): Very good. I still use it and think it is the best, as far as I know.

DR. RICHARD CHUTE (Brookline, Mass.): In the last nine months or so, I have done a couple of these Gersuny-Lowsley-Johnson procedures, and Dr. Goodwin's technique of ureterosigmoid anastomosis is a "natural" for that, because there the lower sigmoid is wide open. I have liked it very much.

CHAIRMAN NESBIT: A great many people have ascribed some of the difficulties encountered with ureterosigmoid anastomosis to the high pressures that are generated within the large bowel. I wonder if anyone has had any experience using banthane or similar chemicals in cases that have a high rectal pressure. Does it relieve the pressure in those cases? Does anyone know?

Are there any other comments about ureterosigmoid anastomosis?

What about the use of colostomy in con-

nection with ureterorectal or ureterosigmoid anastomosis? This will include the discussion of the so-called rectal pouch operation, which has been popular with some.

Dr. Spence, do you want to comment on that?

DR. SPENCE: It seems to me that the principal advantages here, when you get away from the standard ureterosigmoidostomy, is separating the fecal and urinary streams. We can do that by a proximal colostomy. I have thought about doing it as a primary procedure, but in my brief series I have reserved it for the patient who got in trouble over the years. I rather think that is the way I will continue to do it. I mean mostly the hyperchloremic acidosis when I say "getting into trouble." I do not think the acidosis is quite as bad with a colostomy but I don't believe you get away from hyperchloremic acidosis completely.

DR. CORDONNIER: I agree with Dr. Spence on that point. We have had low-grade acidosis in two or three patients upon whom we have done this procedure.

The other point I would like to make, which Dr. Higgins really should be making because he pointed it out a good many years ago, is that one should approach a suprarectal colostomy in children with a great deal of caution, because our experience has been that these children either acquire a huge pouch due to lack of emptying, or little pouches that won't hold anything at all.

DR. HIGGINS: I reported this surgical procedure approximately twenty years ago. I believe that I utilized the technique, mentioned by Dr. Cordonnier, in three patients. One or two years postoperatively, the capacity of the rectal pouch was practically nil, as previously stated by Dr. Cordonnier.

CHAIRMAN NESBIT: Is Dr. Boyce here?

DR. WILLIAM H. BOYCE (Winston-Salem, North Carolina): We are still using it.

CHAIRMAN NESBIT: This is an initial procedure and not a bail-out procedure?

DR. BOYCE: Yes. In 1950–1951 we did an operation on three patients with exstrophy by performing permanent colostomies and vesicorectal anastomoses. We then discontinued this as a primary procedure until the long term results could be evaluated.

Since 1952 we have performed primary closure of the exstrophied bladder in 12 patients (7 at Bowman Gray School of Medicine, 5 at the University of Virginia). The results in these patients have not been encouraging. Urinary continence has been quite satisfactory, but progressive hydronephrosis and pyelonephritis have been a serious threat to renal function.

In the past year we have begun to "bail out" these hydronephrotic patients by establishing a permanent colostomy and vesicorectal anastomosis. The immediate results have been encouraging; however, the course of advanced pyelonephritis cannot always be arrested even in the otherwise anatomically normal urinary tract. For this reason I believe that permanent colostomy and vesicorectal anastomosis should be done as a primary procedure before irreparable renal damage has occurred. The procedure will have its greatest usefulness in the preservation of renal function rather than as a "bail out" measure for the hydronephrotic kidney.

DR. JOSEPH H. KIEFER (Chicago, Ill.): We have used an isolated rectal bladder with colostomy in a couple of bladder carcinomas where there was involvement of the bowel, and they seemed to do better and had less trouble than the ordinary ureterosigmoid in continuity. The urine did not back up into the descending colon.

DR. CARL ABERHARD (Toronto, Ontario): Some eight years ago we did a primary colostomy with a transplantation of the lower segment for carcinoma. We have done none for exstrophy.

There is a series now in Toronto of some twenty-five patients in whom we have deliberately created a colostomy and used the lower segment as the new bladder. We feel that in this way we have avoided two complications—first, severe upper urinary infections, but mostly we feel that by diverting the fecal stream in this fashion we have had much less acid base upset.

CHAIRMAN NESBIT: One of the patients in our series who had a colostomy at the time of the primary procedure went right on and had all the complications, and has died of his urinary tract complications of the transplant, in spite of colostomy and subsequent diversion by another technique.

There was another operation referred to this morning, that of using a rectal pouch and a perineal colostomy. It goes by several names. I wonder if we ought to discuss it.

Dr. Spence, do you have any experience with this procedure?

DR. SPENCE: I am a one-case man. The initial

result was very satisfactory, but the subsequent contracture where the feces came through was a terrific problem, and eventually the patient was bailed out by a proximal colostomy.

I am not in favor of it, but that is on the basis of only one case.

CHAIRMAN NESBIT: I have an idea that this whole panel discussion going on today emanated from some very caustic remarks made by one of our members regarding this procedure. I refer to Dr. Carl Rusche, who was discussing some terrible vicissitudes that were encountered in respect to this particular operation in a hospital where he works in Los Angeles.

There was necrosis of the upper bowel in two or three cases from thrombosis of the mesenterics, and all sorts of other complications.

Do you have any comments to make on this?

DR. HIGGINS: I have had no experience with the procedure.

CHAIRMAN NESBIT: Dr. Kiefer, what do you have to say about this procedure?

DR. JOSEPH H. KIEFER (Chicago, Ill.): We haven't done any more because we have been watching the first group. There have been no bail-outs necessary as yet. The urinary tracts have remained stationary.

We have had trouble with stenosis of the bowel portion, the upper segment brought down which carries the fecal stream. These have required dilatation, and in one case where that was not closely attended to we had quite a bit of trouble. It stenosed almost down to a pinpoint prior to a surgical dilating procedure.

DR. SPENCE: Do they still wear diapers?

DR. KIEFER: The two smaller children we would term continent in the ordinary sense, that is, they void periodically. The youngest is only three years old; we are not certain about the future. There has been a mild acidosis in two of them, subclinical, with no need for any therapy. The chlorides ran 112 or 115, and CO_2 ran 18 or 19 in those cases.

Other than that, the urinary tracts have remained good. Continence is still a moot point, and that is the chief reason why we are holding off doing any more until we can determine the final result.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): We have two cases that have gone for almost a year now. We feel as Dr. Kiefer does, that we don't know enough about it. I agree with him that stenosis of the perineal colostomy is the greatest difficulty.

The other limiting factor is from our conversation with rectal surgeons and general surgeons concerning their experience with perineal colostomies, especially in adults. The defecatory reflex is lost when you remove the distal segment of the rectum, so these patients can urinate readily and are continent in the ordinary sense, but they have difficulty with their bowels. The youngest child had progressive stenosis of her stoma, and required daily enemas to keep her going. That has now been corrected, but it was a difficulty.

Other than trouble with defecation, these patients have no more difficulties than patients with rectal bladders.

I would like to speak for the rectal bladder with colostomy, however formed. Complications have been very few. In our cases, electrolyte imbalance has not been a problem.

CHAIRMAN NESBIT: I suppose if the patient does not have stenosis to hold back the feces, he probably has a tendency to lack control?

DR. HINMAN: No, I don't think that is true. From observation of these patients that isn't so, but they don't know how to defecate. It is a little bit like removing the nerve supply to the bladder neck. Then the patient has to void by straining. Here, the feces move into the rectal ampulla which is now part of the sigmoid brought way down. It produces no ordinary defecating reflex down there, and that then does not stimulate the external sphincter, and so on, and the reflexes in the area to go ahead and empty the bowel. They have perfectly good sphincter tone.

Both openings go through the same sphincter, and if they can hold water they certainly can hold stool. Rather, it is this loss of coordination that they suffer from.

DR. RICHARD CHUTE (Brookline, Mass.): Line for line, one of the most valuable papers I have ever read in my life was written by Dr. Reed Nesbit in the JOURNAL OF UROLOGY for October 1954 on Z-plasty. I have applied Z-plasty to orifices all over the lower part of the body, and in the two Gersuny-Lowsley-Johnsons that we have done I made two zigs in the upper half where you have the perineal colostomy. Although the longest postoperative followup is possibly nine months now, we haven't been bothered by stenosis in either of the cases.

CHAIRMAN NESBIT: Have they been bothered by control?

DR. CHUTE: These patients have had pretty good control. The first is an old man, and the other is a man of 45. They both seem to be getting along pretty well, and are perfectly happy about their control.

DR. RAUL LOPEZ ENGELKING (Mexico, D. F.): We have done the Gersuny procedure in two cases of exstrophy of the bladder and one for ovarian tumor with bladder invasion. We feel that the procedure has had excellent results in the three cases. Patients have done very well in electrolyte balance and urinary and fecal continence.

We did a modification of the Gersuny technique, bringing the sigmoid or new rectum behind the new bladder pouch and in front of the sacrum. We think that by doing this patients might have the sensation of urination that more closely approximates the ordinary sensation since the new bladder will be nearer the abdominal wall and not behind the new rectum. We have made, in the three cases, neocystograms and x-rays of the new rectal pouch in order to watch relationships.

Patients have been very satisfied controlling feces and urine and by gradually training themselves they have learned to know when they want to urinate. We have had one case of mucus formation in the new bladder for a while but this ceased in a few weeks. Another patient had loose bowels for a couple of months but had perfect continence. The third case had, as a result of redundant mucosa, temporary fecal incontinence but perfect urine control. In no case has stenosis developed.

DR. JOSEPH H. KIEFER (Chicago, Ill.): There was a very good article by a rectal surgeon about a month and a half ago concerning the lack of the afferent stimulus which sets up normal defecation reflex.

It is very possible that some patients have this sort of urgency of their bowel when their bladder (the true rectum) fills and starts off bowel activity. Whether re-education will allow them to reassign their reflexes properly, I don't know; but probably the filling of the rectum with urine sets up bowel reflexes on the other side, over which they have less control.

DR. FRANK HINMAN, JR. (San Francisco, Cal.): I would like to raise an etymological point. I think it would be easiest if we all called this operation by the name of its author, Professor Gersuny (1898) and the modification that was described, that of bringing the new rectum down behind, as the Heitz-Boyer and Hovelacque operation. Then we will all be talking about the same thing.

CHAIRMAN NESBIT: Now we come to the belle of the ball. We will discuss the use of the piece of ileum which the three members of the panel choose to call ileal loop diversion. Dr. Cordonnier wants to start off by telling us about a series of 132 cases. He is all in favor of this procedure, but he has been asked to talk rather about the discouraging features which occasionally occur even in his hands, rather than to be a staunch advocate this morning of something we all know he advocates.

DR. HIGGINS: I believe definitely that you should not give up hope for a patient just because grade I or grade II dilatation of the ureters develops. That is no contraindication for reoperation. If the ureters are considerably dilated, and I cannot establish an adequate trough, I prefer to transplant the dilated ureters into the ileum.

DR. MASSEY: Have you had any experience using an everted cuff and using a mucosa-to-mucosa anastomosis and a trough in a primary?

DR. HIGGINS: I have had none.

DR. SPENCE: I have revised a couple of ureterosigmoid transplants and have tried to do that Willy Mathisen nipple deal, and it has worked pretty well. If I were to revise one again I would use the same thing.

DR. BEN D. MASSEY (Pasadena, Cal.): In a couple of cases the patients subsequently died of carcinoma, but we had large, dilated ureters on one side on which we did a cystectomy and we wanted to dispose of the ureter. We used an everted cuff and then made a mucosa-to-mucosa intestinal anastomosis and inverted the cuff of the ureter. They were very successful.

CHAIRMAN NESBIT: Somebody mentioned the Mathisen technique. We used that in a few cases, and we had uniformly poor results with it.

All right, Dr. Cordonnier.

DR. CORDONNIER: First of all, I would like to say that in general the complications we have had, I believe, are due to mechanical failures during this procedure, rather than to any basic difficulty with the procedure per se.

[Slide] This looks like a long slide, and it is, except that I am not going to take your time with all of it.

First, I would like to point out in the early complications that 77 out of our 130 cases had what we would consider no complications at all. Our operative mortality in this particular series (and this is not a blue-ribbon series at all, because it includes all the cases done by the residents in training) was 4.5 per cent, which I think is quite a satisfactory mortality figure. Over half of the cases included a cystectomy.

Our first complication (and one which we feel we have eliminated at least recently) is wound dehiscence, which seems to be a common difficulty. Originally I tried closing these people with wire and everything else, but nothing worked. Now we drain the subcutaneous tissue and, as simple as that sounds, I feel it has been very helpful in preventing wound dehiscence, because we haven't had any in the last forty to fifty cases.

As far as anuria and uremia are concerned, you see we have listed four cases. Of those four, only one, I really felt, was a legitimate case of anuria or uremia. The other three were in cases that were almost hopeless; they were almost in extremis, and we haven't had any hesitancy at all in operating upon an individual who, for instance, has scarring from gold for treatment of cancer of the cervix, and who is rapidly developing anuria and a nonprotein nitrogen output of around 60 or 70, and doing a diversion. We have got by with it in most cases.

Although rare, anuria has been a problem; and, believe me, if they don't start putting out urine within the first 12 hours I begin to worry. If they don't do it within the first 24 hours then we are in real trouble. We have had that happen only two or three times, fortunately.

Tight stoma occurring early, I will discuss in more detail later. I would like to make one point about leakage of urine: In the cases in which it has developed, in most instances if we just let the patient alone, assuming he is not toxic or septic, the leakage will cease spontaneously, as happened in three of the four cases. In the fourth case the leaking ureter was successfully reanastomosed, but in the other three cases we simply let them alone, and they closed spontaneously without a leak. I think that is an important point, because the tendency is to get excited if they leak a little urine.

The rest of these are relatively insignificant complications.

[Slide] In our late complications, the incidence of sepsis, as one would anticipate, has been very low. The important complication—and this to me has been an extremely difficult problem, namely, that in spite of a great deal of care and effort on the stoma, we have experienced difficulty with stenosis. Bricker does not report that difficulty, and I think in all fairness it is because he is not as conscious of drainage as we urologists are. As a matter of fact, he feels that he likes them to be a little on the tight side.

All the trouble we have had has been in patients who have accumulated urine in the segment. When they accumulate urine in the segment or when there is residual urine in the segment, we get into trouble with electrolyte imbalance and all the other things that can happen. Therefore, I think an adequate stoma is very important. If anyone can tell me how to completely eliminate that problem, we will have gone far toward making this procedure even better than we feel it is now.

The incidence of urinary calculi has been surprisingly high. In only one instance was this on the basis of a silk suture that had cut through. In the other four patients calculi developed spontaneously in the kidney. They passed down the ureter, and it certainly was not in direct connection with the operation per se. That is a little disturbing to me.

In three out of some seventy-five patients on whom we did a cystectomy, carcinoma has developed in the urethra, and one wonders if we should do a urethrectomy on these patients as well.

Uremia in three of the four patients was present before the diversion.

As far as our late results on the ureters are concerned, I shall not take a lot of time on this. It is hard to analyze these results. We have tried to be fair. We consider a patient to have an unsatisfactory result if he has dilated ureters and they do not improve. In many cases the operation has been done in late stages with chronic infection. The ureters have been so flabby and so fibrosed and dilated that I don't think they would respond under any circum-

stances; but we still consider them unsatisfactory. In only eleven of our entire series have we felt that our results were unsatisfactory.

I would like to re-emphasize one point Dr. Higgins made, that these patients have to be followed carefully. Operation can be repeated if they don't do well; it is very worth while and not a very difficult procedure to re-do a dilated ureter in a segment. Almost invariably, particularly on the right side, it can be done very simply. On the left side you have to end up by going through the mesosigmoid, which is somewhat difficult technically.

In general, we have improved 21 cases. The number of patients who were good preoperatively is not so great as those in the followup, and likely the number of poor cases preoperatively is definitely less than the latter ones. In other words, we have definitely improved thirty-one of these, and some of them were very poor to begin with.

DR. BAKER: Mr. Chairman, my remarks will be confined to the complications and unfavorable results of the ureteroileal conduit for diversion of the urinary stream in some forty patients during the past three years.

Mr. H. S., aged 63, was subjected to ureteroileostomy and cystectomy with prostatovesiculectomy for carcinoma of the urinary bladder in December 1957. His convalescence was slow. He experienced recurrent febrile episodes. He was sent home. He noted pain in his left flank on the 48th postoperative day. This was the first indication of renal disease. [Slide] This is a roentgen study of the abdomen which shows an opacity on the left at the level of the fourth lumbar vertebra. The opacity was not present in the postoperative urograms six weeks previously. [Slide] Here is a roentgen study which localizes the opacity to the left ureter, by retrograde pyelography, when a radiopaque substance was injected into the ileal conduit. An extraperitoneal ureterolithotomy was done. The patient has had no further febrile episodes and feels well.

Mr. G. C., aged 66, was so miserable from his small capacity bladder due to interstitial cystitis, that an ileal conduit was made to divert his urinary stream in January 1958. His postoperative course was normal for 14 days. Then extreme sepsis developed. He complained of no pain or tenderness. [Slide] Here is a retrograde pyelogram which was made by injecting the conduit. There is obvious extravasation of the radiopaque medium in the region of the right ureteral anastomosis with the conduit. Right nephrostomy and drainage of the extravasated area relieved an extremely septic patient. He made a remarkable recovery. He does, however, wear a right nephrostomy tube and a bag over the stoma of the ileal conduit.

Mrs. M. S., aged 44, had an ileal conduit made and a cystectomy done for carcinoma of the urinary bladder in November 1956. She made an uneventful convalescence and remained well for 6 months. Then she complained of right flank pain, recurring chills and fever. [Slide] Here is an intravenous pyelogram that was made at this time. Right hydro-ureteronephrosis is present. It was decided to revise the right ureteral anastomosis. Surgery disclosed an acute angulation of the right ureter in the scar where the ureter was brought through the peritoneum. The anastomosis of the ureter to the ileal conduit was quite patent. The ureter was divided proximal to the acute angulation and reanastomosed by bringing it anterior to the mesentery of the ileal conduit. This stopped the back pain, chills and fever. However, she died of carcinomatosis a few months later.

Mrs. A. M., aged 49, had her urinary stream diverted by an ureteroileal conduit, followed by cystectomy for squamous cell carcinoma of the urinary bladder. Convalescence was prolonged by a low-grade fever and recurrent enteritis and much watery diarrhea. She survived for 9 months before she succumbed to carcinomatosis. [Slide] This is an illustration of what was found at autopsy. At the site of the end-to-end anastomosis of the ileum and on the anterior surface of the midportion of the conduit, there was a patent fistula between the bowel and the conduit. This fistula was 2 mm. in diameter and 3 cm. long. The fistulous tract was epithelialized and surrounded by much scar tissue. The fistula and the surrounding area were free of tumor tissue.

The foregoing complications have not dampened our enthusiasm for this method of diverting the urinary stream. It has brought comfort to most of our patients.

TUBERCULOSIS IN A SOLITARY KIDNEY

JOHN K. LATTIMER

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Modern chemotherapy has greatly improved the outlook for the patient who has tuberculosis in a solitary kidney. Nevertheless, great care must be exercised so that the drugs will be correctly used, since the first course of treatment will have by far the best chance of success. If, for instance, the drugs are taken in inadequate doses, so that drug resistance develops, the outlook will again become grave. Other limitations, such as the development of intolerance to one or more of the drugs may also interfere with successful treatment. While we have two excellent drugs (streptomycin and isoniazid) both of the first order of effectiveness, we only have one proven drug of the second order of effectiveness (sodium para-amino salicylic acid) with which to supplement the first two.

We have several drugs of the third order of effectiveness, such as cycloserine, viomycin, promizole and the thiosemicarbasones, but these medications are relatively ineffective and relatively toxic. We have additional drugs, such as pyrizinamide, which are useful for only a short period, before drug resistance develops. However, pyrizinamide is too hepatotoxic for general use. New drugs such as kanamycin, and thiocarbanidin are now being tested, but may not be drugs of the first order of effectiveness.

Since this large number of drugs is available to us, it is usually possible to arrange a therapeutically effective regimen by using combinations of these medications to accommodate to any special requirements of any particular patient. However, since so many drugs are involved, with so many different possible toxic actions, it is sometimes difficult to be sure that the optimum treatment is being given. One of the greatest hazards is the fact, mentioned above, that dosages which the patient will tolerate may not be therapeutically effective, merely leading to the rapid development of drug resistance, without arresting the tuberculosis.

This work has been supported in part by a grant from the National Tuberculosis Association, whose help is appreciated, as is that of the staffs of the Squier Clinic and the Kingsbridge Veterans Administration Hospital.

In the patient with a solitary kidney, decreased renal excretion may lead to the accumulation of toxic blood levels of certain drugs, such as isoniazid and cycloserine, which stimulate the central nervous system, with resulting convulsions, even at conventional dosage level.

With the uremic patient, it is necessary to do drug blood levels in order to make sure that toxic amounts of these drugs are not accumulating. Another factor which must be considered is the age of the patient. For instance, streptomycin will cause permanent ataxia in elderly patients while dihydro-streptomycin will cause permanent deafness in elderly patients, whereas in younger patients neither of these toxic manifestations may occur. To counteract these possibilities, there are available preparations which are combinations of half streptomycin and half dihydro-streptomycin.

STANDARD CHEMOTHERAPY REGIMENS

Triple drug therapy, employing streptomycin 1 gm. twice weekly, isoniazid 100 mg. three times daily, and sodium PAS 5 gm. three times daily, for a period of one year, has been the most effective regimen we have tested to date. Out of a test group of 52 patients with advanced, cavitary, renal tuberculosis, only two have relapsed following one year of treatment with three drugs, and neither of these was a complete failure for this regimen. One patient spilled one isolated positive urine culture, four years after the beginning of treatment and the other patient had acquired drug resistance prior to the initiation of triple drug therapy. By contrast, from our group of 64 test cases that were treated with two drugs (streptomycin and PAS), for one year, there was a total of 10 failures at the four-year point in time, after the beginning of treatment, as compared with only two failures in the triple drug group. While these differences in effectiveness may not appear to be statistically very significant at this time, the superiority of the triple drug group has been consistent in three different groups of patients where the

results have been studied. An alternative regimen, combining isoniazid and sodium PAS for periods of one or two years has been widely advocated for the treatment for pulmonary tuberculosis, in preference to the triple drug regimen. However, in our cases of advanced kidney tuberculosis, the INH-PAS regimen has not yielded quite as good results as the triple drug regimen, at least for advanced cavitary kidney tuberculosis. It is our practice to use the two drug regimen (isoniazid-PAS) for kidney lesions which do not show cavities by x-ray, but where the urine culture is positive for Mycobacterium tuberculosis. We regard these tuberculous lesions as being "minimal" and expect them to respond to the two drug regimen. We also use the INH-PAS regimen before and after any surgery which we may perform on the urinary tracts of patients with tuberculosis.

STRICTURE OF THE URETER IN SOLITARY KIDNEYS

One of the greatest dangers from tuberculosis in a solitary kidney is the possibility that stricture of the ureter may develop. It is our feeling that these strictures usually arise where some tuberculous granulations have already existed, and that the healing of these granulations is expedited by chemotherapy so that strictures may tighten rapidly during chemotherapy. We do not believe that chemotherapy causes strictures of the ureter; it merely hastens the tightening of collagenous scar tissue in the bases of tuberculous granulations which are already present. In any case, we regard it as essential that intravenous pyelograms be performed every four months during chemotherapy and that size 6 ureteral catheters be passed up through the ureter at least every four months during chemotherapy in order to guard against stricture formation. After therapy terminates, these intervals may be increased to every six months. If there is any sign of stricture, cystoscopic dilatations may suffice to keep the stricture open until chemotherapy heals the lesions. If cystoscopic dilatation fails, then open ureterotomy with intubation of the stricture may help, or urinary diversion may become necessary. It is our preference to employ cutaneous ureterostomy with a split thickness skin graft wrapped around the ureteric bud and a cup glued over the bud, rather than a catheter in the kidney. It is our practice to provide our patients with a bougie with which to dilate the ureteral stoma at weekly intervals to make sure that no stricture forms there. We prefer not to use nephrostomy because of the necessity for a tube in the kidney, which is an inducement for stones to form, and because of the inconvenience and danger of frequent tube changes. Nevertheless, permanent nephrostomy is necessary in occasional cases. Ureterosigmoidostomy is apparently not advisable for most cases of genitourinary tuberculosis. While we have not done this operation ourselves, we have knowledge of approximately 20 cases where this has been done and all patients but one have died within one year after operation. We know of one in whom the remaining kidney was free of tuberculosis at the time it was implanted in the colon, and this patient is doing satisfactorily.

REFLUX IN TUBERCULOUS URETERS

Another hazard of old tuberculosis of the bladder is that the ureterovesical junctions may become fibrosed by contracture or disease of the bladder, which may have healed, but has left the ureterovesical valve incompetent. Whenever a bladder is contracted from tuberculosis, it is very probable that there will be reflux up the ureters, in our experience. The resulting back pressure against the kidney may be harmful, especially if the kidney is infected. While the patient may be able to relieve the pressure on the kidney by frequent voiding, plus triple voiding to completely empty the pelvis, these patients must be watched closely so that cutaneous ureterostomy or other diversion can be employed if the kidney begins to deteriorate.

SUMMARY

Tuberculosis in a solitary kidney is best treated by combinations of drugs given over periods of one to two years. Some of the drugs used for the conventional treatment of renal tuberculosis may not be suitable for patients with diminished renal function in a solitary kidney, because of the accumulation of toxic blood levels of these drugs. For these patients, special combinations of chemotherapeutic drugs may be necessary to accommodate to their particular needs. The appropriate drugs can be selected from the armamentarium now available. Additional new drugs are now being tested.

Special care must be taken to detect strictures of the ureter which may tighten down more quickly during chemotherapy. The solitary kidney must be protected against back pressure from reflux, in case of destruction of ureterovesical valve which often results from fibrosis of the tuberculous bladder. Chemotherapy has greatly improved the outlook for the patient with tuberculosis in a solitary kidney. Triple drug therapy (SM-PAS-INH), prescribed at least one year, is an effective regimen for most patients with kidney tuberculosis.

Semi-ambulatory bed rest is advised for these patients during the first six months of chemotherapy and therapeutic vitamins are administered throughout the therapy. *Pyridoxine* 50 mg. twice daily must always be given to patients receiving *isoniazid.*

HYDRONEPHROSIS: ITS TREATMENT IN THE SOLITARY KIDNEY

THOMAS E. GIBSON

In the same category with patients who have only a single or solitary kidney should be included those who have an opposite hypoplastic kidney, or a kidney crippled by any disease which would render it incapable of sustaining life by itself. We must therefore broaden our concept of the single kidney to include such cases, because failure to adequately cope with the problem of the hydronephrotic kidney would have equally disastrous results. The presence of an opposite normal kidney engenders some feeling of security, but in the single kidney we cannot afford a failure because it could easily result in the death of the patient. The management of hydronephrosis in the single kidney therefore imposes an especially grave responsibility upon the urologist.

The surgical correction of ureteropelvic obstructions in the single kidney in my early experience was approached with a great deal of trepidation, especially so in those desperate cases with advanced lesions accompanied often by gross infection and elevated blood chemistry. In retrospect, several cases of this type come to mind which were in such desperate plight that in some instances they were practically moribund. The fact that there has been no surgical mortality in this group and that they are now living and well is a testimonial to the wonderful recuperative powers of the single kidney even under the gravest handicaps. The amazing recovery of these patients has led me to believe that the single kidney, through force of necessity, has a greater power of recovery than a similar kidney that has a normal mate. Proof of this interesting observation has recently been produced by Edwards, Maher, and Grindlay of the Mayo Clinic, who studied the histopathology of the kidney and its recovery following severe renal ischemia. In a series in which the opposite kidney was preserved intact, there was an average weight loss of 17 per cent in the damaged kidney, whereas, if contralateral nephrectomy was performed there was an average increase in weight of 80 per cent. Histopathologic evidence supported Hinman's original theory of renal counterbalance which in essence states that a damaged kidney capable of recovering will do so proportionately to the amount of recovery demanded of it.

This concept, as well as advances in surgical technique as applied to the treatment of hydronephrosis, has largely dispelled our earlier fears, so that we now attack problems affecting the single kidney with relative equanimity.

The literature on the surgery of hydronephrosis has grown to extensive proportions in the last 20 years. Of particular importance has been the experimental aspect of the problem sparked by the epochal contributions of Davis and his associates on ureteral regeneration and repair, an understanding of which is so necessary in the successful treatment of hydronephrosis. However, there are problems involved in plastic operations to correct ureteropelvic obstructions which do not lend themselves readily to experimental research in animals, so dependence on the slower processes of clinical experience has been necessary to their solution.

The history of plastic operations for the correction of ureteropelvic obstructions dates back to the original operation of Trendelenburg who in 1886 sought to correct a case of high insertion with valve effect by incising the junction downward with lateral anastomosis of ureter and pelvis. Further experience with this procedure resulted in a high percentage of failures, as did also the subsequent procedure of Kuester, which consisted of cutting the ureter off squarely and reimplanting it in the pelvis, and that of Fenger consisting of longitudinal incision and transverse closure according to the Heineke-Mikulicz principle. It was found that Trendelenburg's operation did not produce adequate dependent funneling. Kuester's operation too often resulted in circumferential stricture at the site of anastomosis, while that of Fenger often caused buckling of the ureteropelvic junction with subsequent obstruction.

These procedures were rendered obsolete by the epochal contribution of Foley in 1937. His Y-plasty is a flap operation which combines the three essential features or principles necessary for a successful result, namely, the avoidance of shortening by the suture line, correction of high insertion of the ureter so as to obtain dependent

drainage, and gradual funneling of pelvis into ureter.

The soundness of Foley's concept is attested by the fact that it, or some modification of it, is the most widely used operation at the present time. Although there are many ingenious flap operations in use at the present time (Bischoff, Culp and De Weerd, Scardino and Prince, Anderson and Hynes, Gardner, Lich), they are all based on the original Foley operation. Even the present version of the original Kuester operation, which now is widely acclaimed and consists in excision of the pelvis and upper ureter with reanastomosis of a pelvic flap and spatulate ureter, as recommended by Nesbit in his elliptical anastomosis, is in reality a "dismembered Foley" as stated by Webb, Smith and Price, and for the sake of terminology should be referred to as such.

In 1943 an entirely new concept in the treatment of ureteropelvic obstructions was promulgated by Davis with his operation of intubated ureterotomy. This operation consisted in simple longitudinal incision of the strictured area and avoided the necessity for elaborate plastic procedures as well as sutures by emphasizing the importance of intubation or splinting. Nephrostomy or pyelostomy drainage was a necessary corollary to this procedure. Hamm advocates the Davis principle of simple longitudinal incision in uncomplicated cases, but a vent in the pelvis without intubation.

The Davis operation vied in popularity with the Foley operation, and led to considerable diversity of opinion with particular respect to the role of intubation or splinting. The relative merits of intubated ureterotomy (Davis) versus sutured pelvioureteroplasty (Foley) were often a matter of debate, but increasing experience has reconciled views on these vital problems and shown that there are definite indications for both procedures.

In earlier experience, the author felt that splinting was necessary in all operations for the correction of ureteropelvic obstructions. Indeed, it was felt that this was the most important factor of all in achieving a successful outcome. It was not until the work of Hamm and Weinberg that this attitude changed, but not without some misgivings. Theoretically, the ideal operation is one in which splints and drains with their attendant morbidity, however slight, could be avoided. Experience has been gratifying in showing that this can be accomplished in suitable cases by resorting to the use of a simple vent in the pelvis, with the entire omission of splinting or intubation as well as nephrostomy or pyelostomy drainage tubes. Davis has recently published a scholarly review of the subject which is recommended reading.

As a summation of conclusions reached after thirty years of experience with a problem that has been the subject of special personal interest, the operative procedures which have emerged as best suited to the vast majority of ureteropelvic obstructions are as follows:

1) Block excision of pelvis with flap anastomosis (Bischoff) (fig. 1).

2) Dismembered Foley (fig. 2).

3) Intubation ureterotomy (Davis) (fig. 3).

Procedures 1 and 2 are personally favored and are used more or less interchangeably. They are both flap operations based on the original Foley Y-plasty. Generally, splinting is avoided in favor of a simple vent in the pelvis. However, a splint is used if conditions are not considered favorable for its omission. I feel that in the presence of infection, scar tissue formation or evidence of impaired blood supply that splinting is necessary. In younger people with congenital obstructions and no infection, intubation can be omitted. Avoidance of splinting promotes a shorter and more comfortable convalescence.

The intubated ureterotomy of Davis, in which splinting is of primary importance, is now reserved for certain specific conditions. I believe that it is the procedure of choice, if not actually mandatory, in the following conditions:

1) Where the ureteropelvic junction is badly scarred as a result of previous operation.

2) In the presence of marked inflammatory changes in and about the ureteropelvic junction.

3) In cases of partial or complete separation or avulsion of kidney pelvis and ureter as a result of previous surgery or injury.

4) In patients approaching or past middle age where there may be delayed healing.

5) Where there are multiple or unusually long constrictions.

The following brief case reports illustrate some extreme examples of the problem of hydronephrosis in the single kidney:

Case 1: Female, age 25 years. Acute fulminating colon bacillus pyelonephritis of congenital

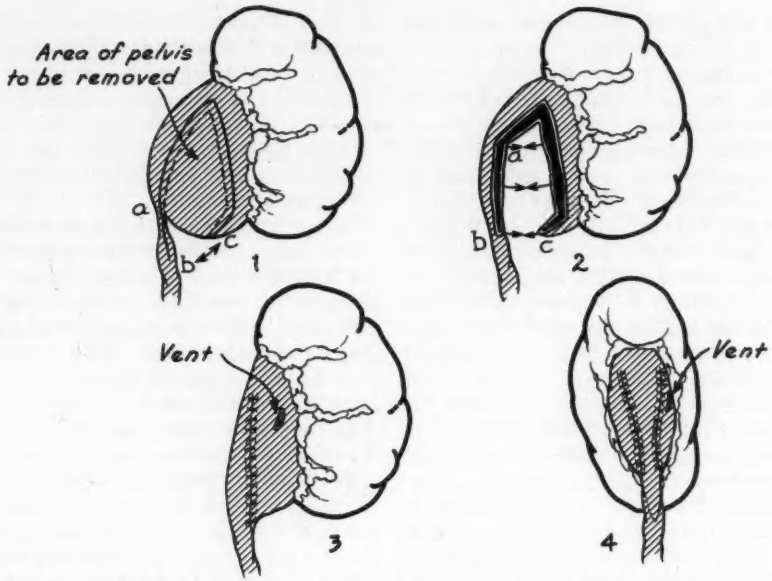

FIG. 1. Bischoff pelvioureteroplasty utilizes same principles as dismembered Foley except that ureter remains attached to pelvis. Block excision of redundant pelvis is accomplished, followed by pelvic flap anastomosis.

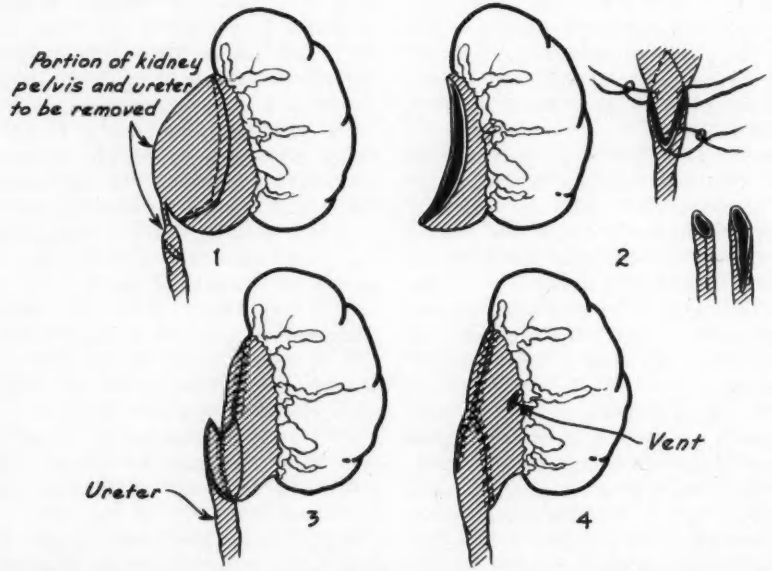

FIG. 2. Dismembered Foley operation. Complete excision of pelvis and ureteropelvic junction. New ureteropelvic junction is created by elliptical anastomosis of ureter to pelvic flap. Vent drainage or intubation as surgeon desires or as case indicates.

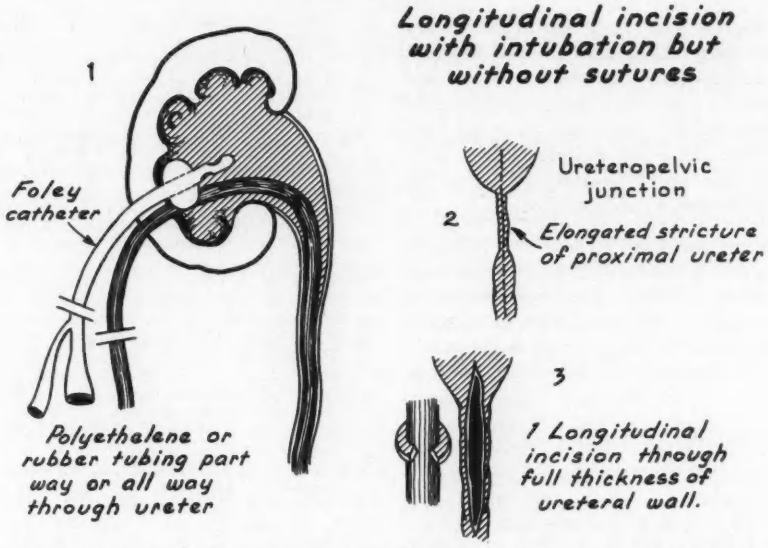
Longitudinal incision with intubation but without sutures
1
Foley catheter
Polyethalene or rubber tubing part way or all way through ureter
2
Ureteropelvic junction
Elongated stricture of proximal ureter
3
1 Longitudinal incision through full thickness of ureteral wall.

FIG. 3. Davis intubated ureterotomy. Simple longitudinal incision of constricted area with intubation and either nephrostomy or pyelostomy drainage.

solitary left kidney. Fever, chills, elevated blood chemistry. Patient moribund. Emergency nephrostomy. Intubated ureterotomy 3 weeks. Complete recovery. Recheck after 4 years revealed normal pyelogram, sterile urine, PSP (intravenous) output 1 hour, 60 per cent.

Case 2: Female, age 24 years. Congenital solitary right kidney with chronic infected hydronephrosis of giant proportions causing marked bulging of right side of abdomen. Patient acutely ill with fever and elevated blood chemistry. Unable to pass catheter to pelvis cystoscopically. Emergency nephrostomy with intubated ureterotomy. Patient seen in hospital 5 years later following injury in automobile wreck. Kidney functioning well and blood chemistry normal, but still evidence of chronic low grade infection.

Case 3: Female, age 19 years. Bilateral hydronephrosis with uremia. Right kidney contained 3500 cc fluid. No function. Right nephrectomy done. Left kidney 350 cc capacity with stricture of ureteropelvic junction. Davis type intubation carried out using T-tube, one limb extending down ureter, the other running up into pelvis. The ureteropelvic junction was incised longitudinally and likewise a second narrow area about one inch below the pelvis. Splinting maintained for 3 weeks. Excellent result. When seen 4 years later the patient was married and had 3 children.

Case 4: Female, age 32 years. Mother of 3 children. Congenital hypoplastic right kidney. Left kidney large, infected, hydronephrotic, thin-walled sac with relatively little parenchyma. Blood chemistry elevated. "Dismembered Foley" procedure was carried out, without intubation. However, in view of the fact that this patient was dependent upon this one kidney for survival, a nephrostomy drain (24 Foley catheter) was used. The patient was out of bed on the second postoperative day and the drain was clamped off most of the time. In spite of this, healing was per primam and the patient made an excellent recovery. In spite of the small amount of parenchyma present, her blood chemistry dropped to normal and the infection cleared up.

CONCLUSIONS

Progressive impairment of function in a solitary kidney which is hydronephrotic, regardless of the presence or absence of associated pain or infection, calls for summary correction.

Special care must be exercised in choosing the proper surgical procedure since the survival of the patient depends on its successful accomplish-

ment. The fact that the single kidney seems to respond better than the one with a normal mate in conformance with the theory of renal counterbalance often leads to surprisingly good results even in the most discouraging cases.

The choice of operative procedure and indications for the use of splints and drains, as well as their omission, are discussed.

It was my privilege to converse with Mr. Anderson this summer in London, and to learn that in his use of the operation of ureteroneopyelostomy (dismembered Foley) he uses no splints or drains, not even a vent in the pelvis. This water-tight closure has given him excellent results.

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INJURY OF THE SOLITARY KIDNEY

ROBERT LICH, JR.

Successful treatment of renal injuries must be governed by certain fundamental principles in spite of the fact that the literature presents figures which would seemingly justify methods that are at complete variance. These principles must further be augmented by, as Dr. William W. Scott once said, "a large measure of common sense. . . ." However, in the instance of the injured solitary kidney additional measures are necessary to recognize and treat the variable degree of renal dysfunction which is commonly associated with renal trauma.

Fortunately, congenital solitary and hypoplastic kidneys occur no more frequently than 1:600 and 1:500 respectively. During the past 25 years, at the University of Louisville School of Medicine not a single case of injury in a solitary kidney has been recorded in spite of the fact that over one thousand urinary tract injuries have been seen and of that group, 242 renal injuries. In our own practice two such cases have been seen, both in consultation.

Before delving into the therapeutic problem of the injured solitary kidney a few general facts must be appreciated. The congenital solitary kidney is often associated with other anomalies and particularly of the urinary tract. Such abnormalities as pyelectasis, renal duplication, ectopia, ureteral duplication, atonia with ureteral dysfunction could readily influence successful therapy. Furthermore, urosepsis in the single kidney is more common and infection superimposed upon trauma may cause a severe, if not fatal, complication unless it is given adequate consideration in the initial plan of treatment.

In renal trauma the immediate problems are: 1) shock and 2) hemorrhage. Shock must be dispelled promptly and its specific cause demonstrated. As soon as the shock state is corrected excretory urography is essential to ascertain the extent of renal trauma and the presence or absence of the opposite kidney and its functional capacity. If for any reason diagnostically inadequate films persist a retrograde urogram is mandatory. The often quoted fear of infection from retrograde urography in renal injury is not nearly so hazardous as an inadequate diagnosis. It is at this time that the presence of an injured solitary kidney may become manifest and this discovery may be life saving.

In the presence of a renal contusion without evidence of urinary extravasation and renal bleeding which does not affect the blood volume, conservative therapy, consisting of absolute bed rest for at least seven days, should follow the disappearance of gross hematuria. Earlier ambulation may increase the incidence of delayed bleeding which may occur some 10 to 12 days after injury. In the solitary kidney this therapy must be supplemented with careful observations of kidney function so that any dysfunction is immediately recognized and measures taken to avoid overhydration, and electrolyte imbalance. The appearance of ileus should be treated early so that its inherent physiologic upset can not induce or increase the already present renal dysfunction. In short, the patient with but a single kidney in the face of trauma to that organ must be given every consideration which is both directly and indirectly referable to the renal status and renal load.

Whenever renal trauma is associated with severe renal bleeding and/or disruption of the continuity of the intrarenal drainage system with or without evident perirenal extravasation, surgical exploration is indicated. Immediate rather than delayed renal exploration should be the rule since the earliest possible repair of injured tissue is a fundamental surgical principle. The condition of the tissues and healing are optimal at this time.

The purpose of surgery should be 1) ligation of individual bleeding vessels, 2) control of surface bleeding, 3) removal of intrapelvic clots, 4) adequate urinary drainage, 5) determination of associated ureteral injury, 6) cultural studies and 7) restoration of normal renal morphology with the obliteration of dead spaces between renal fragments.

After ligation of the individual bleeding vessels the renal surface bleeding can usually be controlled by the use of perirenal fat interposed between the torn kidney surfaces and maintained by adequately placed mattress sutures. The renal pelvis should be opened to

remove any clots and at the same time afford good urinary drainage. Pyelostomy would seem generally more safe than nephrostomy in this particular situation, but circumstances will often make this descision at the operating table. The ureter must be visualized to eliminate unsuspected injury to this vital structure.

Intrarenal cultures should be taken to indicate the most effective postoperative antibiotic or chemotherapeutic agent. As mentioned previously, this is particularly important in the solitary kidney due to the increased incidence of chronic infection. The seriousness of delayed post-trauma infections is well documented and can easily afford a fatal complication in an injury of a solitary kidney.

Following surgery the renal functional status of the kidney must be observed meticulously with particular attention to avoid an imbalance between hydration and urinary excretion. Furthermore, electrolyte studies are mandatory to observe renal activity and in the event of serious progressive imbalance, measures to reestablish a near normal electrolyte pattern during the phase of temporary renal dysfunction are essential. A simple procedure, that may be used early with effectiveness, is continuous gastric lavage although it is conceivable that it may be necessary to rely on dialysis, the great hazard of dialysis being of course additional renal bleeding due to the necessity of using an anticoagulant. In considering dialysis progressively increasing potassium value of the blood should serve as the indication rather than the degree of azotemia.

SUMMARY

In treatment of the injured solitary kidney the surgeon must avoid any risk which might well be taken with an injured kidney wherein an opposing normal kidney exists. The specific risks in this unusual situation are infection and temporary renal dysfunction. It is with these factors in mind that renal exploration is essential in every instance other than the most insignificant renal contusion; even there prophylactic antibiotic or chemotherapeutic therapy is essential since the incidence of renal infection is greater in the solitary kidney and the hematoma associated with injury affords a medium which might well permit a delayed disastrous suppurative destruction of the available renal tissue.

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DISCUSSION

DR. GERSHOM J. THOMPSON (Rochester, Minn.): I should like to speak briefly about another disease of the solitary kidney, namely, neoplasm.

An operation such as partial nephrectomy in the face of neoplasm should be justified by the hope that the lesion is in fact amenable to partial resection, but it can also be justified on the possibility and probability in some cases of spontaneous regression of cancer.

I refer to the fact that even in the face of apparently hopeless situations which we have encountered in the past, such as the presence of tumor thrombi in the renal vein which cannot be removed, one thinks this operation can't possibly effect a cure, yet some of these patients live fifteen to twenty years or more.

On the other hand, in the case of a small tumor in the kidney wherein nephrectomy should provide an excellent chance of cure, the patient might instead go to an early death.

I commend for your perusal at some convenient time an article by William Boyd, the pathologist in Toronto, on "The Spontaneous Regression of Cancer", which appeared in the September 1957 JOURNAL OF THE CANADIAN ASSOCIATION OF RADIOLOGISTS, and the second part of it appearing in the December issue.

We have seen at the clinic a number of cases in which tumors did develop in solitary kidneys.

[Slide] We felt warranted and justified in doing a partial nephrectomy in this case, a 41-year-old wife of a physician who came with a mass in her kidney that she had known had been present for over a year. She and her husband had hoped it was a cyst. We hoped so too, but the lesion was explored with a view to doing a partial nephrectomy if it proved to be a tumor.

This is the postoperative urogram made some four months later.

[Slide] This shows the way the tumor was excised. It was cut straight across. There was no dissection of the capsule.

[Slide] This is the portion that was removed, showing the clean-cut nature of the renal tissue at the point of incision.

[Slide] This shows the mass itself, which weighed 650 gm. This patient went on with the thought that the tumor had been successfully removed. We hoped it had been. There was no recurrence locally, but she did have pulmonary metastasis from which she died a year and a half later. She bled from an extensive pulmonary hemorrhage from this metastatic area.

[Slide] This is the case of a woman who had a tumor in her left kidney, which had been removed elsewhere. The surgeon had done this operation in two stages. He had removed a tumor from the end of the kidney, then got fainthearted about it and decided to remove the entire kidney. She came to the clinic subsequently with pain in the right side, and we found a deformity of the lower calyx. The kidney was explored.

[Slide] A tumor of the lower pole of the kidney was found and was excised.

[Slide] The tumor was completely excised. It proved to be a cystadenoma.

[Slide] This shows the tumor cut open. This was in fact a relatively benign grade I cystadenoma.

[Slide] This next case is a woman of 43 years of age who had a hypernephroma, 5 by 4 by 4 cm., of the kidney. This was excised. Subsequent exploration was done of the abdomen for abdominal hysterectomy. At that time there was no recurrent tissue anywhere. She was seen for the last time last October and was perfectly well.

[Slide] This is a 61-year-old man who came with a solitary kidney, with a papillary epithelioma in the renal pelvis. This kidney was opened and the tumor removed. The underlying area was electrocoagulated. This case was reported previously by Ferris in the JOURNAL OF UROLOGY.

[Slide] This is a slide of a man who came with a left hypernephroma which we removed, and some six months later he returned complaining of hematuria. At that time retrograde studies of the right kidney seemed to be entirely normal. Bleeding was thought to be coming from his prostatic urethra. However, he returned a month or so later with bleeding from the right ureteral orifice.

At that time an obstruction in the middle third of the right ureter was found. This was a metastatic hypernephroma attached by a slender

stalk to the ureter. It was excised locally. A T-tube was put in, and since then there has been no recurrence.

I think these cases point up the thought that even in the face of neoplasm one is justified in doing a partial nephrectomy in the hope of cure. Three of these patients are still alive, and two are deceased.

DR. VINCENT J. O'CONOR, JR. (Boston, Mass.): If I may, in Dr. Harrison's absence, I might give you a couple of points that we feel are pertinent to this problem.

First, with regard to heparinization in dialysis, we have had very little experience in using intermittent heparinization; however, it is a method of dialysis which is useful in treating patients who have either gastric bleeding or bleeding from another source. Briefly, the method consists of using heparin in the inflow tract, going to the artificial kidney and protamine on the venous side going back into the patient.

The one thing which I want to point out in regard to surgery of the solitary kidney is that frequently these patients who are uremic are under an osmotic diuresis, in other words, the ones with only one kidney, do tend to lose a large amount of sodium in the immediate postoperative period. This phenomenon should be anticipated in surgery of the solitary kidney and early replacement carried out rather than withholding saline for the first few postoperative days as is the custom in the absence of extrarenal losses.

CRYSTAL-MATRIX INTERRELATIONS IN CALCULI

WILLIAM H. BOYCE AND J. STANTON KING, JR.

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The organic matrix of all urinary calculi is a mucoid.[1] The origin of this matrix is not clearly established. The amino acid and carbohydrate composition of stone matrix is so similar to an insoluble urinary mucoid, uromucoid, as to suggest that matrix is derived from this substance.[2, 3] However, urine contains many soluble proteins which also contain the carbohydrates found in stone matrix.[4, 5]

Stone matrix exists in two microscopically distinguishable forms, fibrous and amorphous.[1] The amorphous matrix is much more soluble in dilute salt solutions than uromucoid. Trace amounts of lipid have been found in association with uromucoid, but not in stone matrix. The matrix from which apatite has been removed by decrystallization is highly metachromatic with aqueous toluidine blue-O, whereas other matrix is commonly orthochromatic. The glucose content of matrix from pure uric acid calculi is appreciably less than that of calcigerous calculi. Minor variations in structure of such large complex mucoid molecules may produce profound changes in physicochemical characteristics without producing compositional changes which are detectable by currently available analytical techniques.[6]

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[1] Boyce, W. H. and Garvey, F. K.: The amount and nature of organic matrix in urinary calculi: a review. J. Urol., **76:** 213–227, 1956.

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[5] King, J. S., Boyce, W. H., Little, J. M. and Artom, C.: Total nondialyzable solids (TNDS) in normal human urine. I. The amount and composition of TNDS from normal subjects. J. Clin. Invest., **37:** 315–321, 1958.

MATRIX CALCULI

Eleven patients with urinary calcium excretion rates less than 40 mg./24 hrs. have formed poorly crystallized roentgenolucent renal calculi. Six of these patients had severe impairment of renal function as a result of advanced chronic pyelonephritis and partial urinary obstruction. Five patients formed these matrix calculi while on a low calcium-low vitamin D-high phytate regimen, with supplemental sodium phytate.[7] Several of the largest such calculi are depicted in figure 1. Analyses of these calculi have indicated that their essential difference from calcigerous calculi is in the crystal: matrix ratio (table 1). In fully crystallized calculi the matrix accounts for 2.5 per cent of the dry weight, but in "matrix" calculi the comparable average is 65 per cent with a range of 42 to 84 per cent of the dry weight.

The low crystalline content of matrix calculi has permitted microscopic and histochemical studies with no treatment other than fixation in neutral formalin.[2] The crystal-matrix interrelations have been the same in specimens from all eleven patients. A typical example is shown in figure 2.

The matrix is uniformly present throughout the calculi. Laminations of dense matrix surround the center of the calculus in a series of more-or-less regularly spaced intervals. Serial sections indicate that each lamination is a membrane, retaining its integrity in complete envelopment of the center and all subjacent laminations. The most central lamination may be so eccentric as to approximate the surface of the concretion, but there is always an equal

[6] King, J. S. and Boyce, W. H.: Amino acid and carbohydrate composition of the mucoprotein matrix in various calculi. Proc. Soc. Exp. Biol. & Med., **95:** 183–187, 1957.

[7] Boyce, W. H., Garvey, F. K. and Goven, C.: Abnormalities of calcium metabolism of patients with "idiopathic" urinary calculi: effect of oral sodium phytate. J.A.M.A., **166:** 1577–1583, 1958.

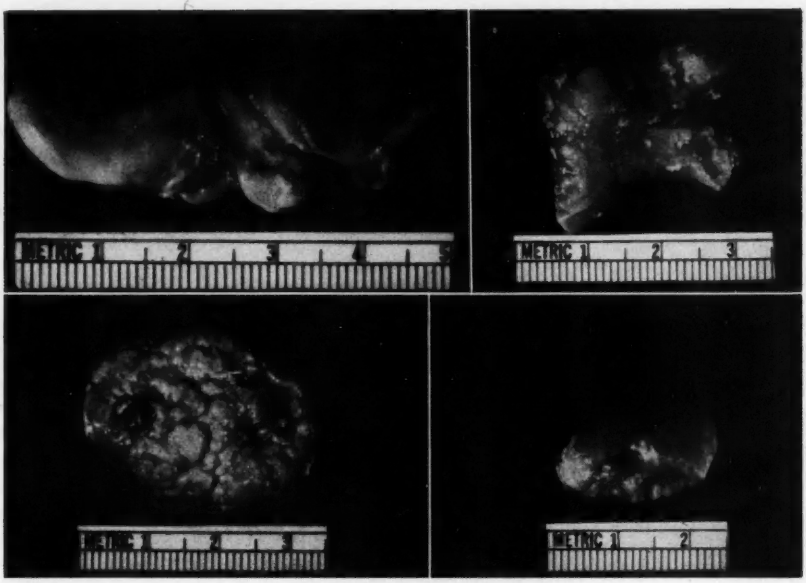

FIG. 1. Roentgenolucent "matrix" calculi

number of laminations peripheral to it. Where the most central lamination is nearest the surface, the surrounding membranes are in close approximation, gradually separating to a maximal spacing where the most central lamination is farthest from the surface.

Amorphous matrix fills the spaces between laminations. In some areas there are small "pockets" of fibrillar matrix which may be completely unoriented with respect to one another (fig. 2, *G*). In other calculi these small pockets may become oriented into spherules of concentric laminations which suggest secondarily formed calculi entrapped within the main body of the stone.

CONVENTIONAL "FULLY" CRYSTALLIZED CALCULI

The methods for preparing plastic mounts of microscopically thin sections of fully crystallized calculi and their study by microradiography, polarographic microscopy, decrystallization, and histochemistry have been described.[8, 9]

MATRIX AS A DETERMINANT OF CRYSTAL POSITION

Crystal deposition has *not* been uniformly distributed from center to surface in any calculus. Variations in crystal density are invariably related to the laminations in the matrix. In no section of a calculus has there been a wedge of uniform crystal deposition extending uninterruptedly across contiguous laminations.

Many laminations in matrix calculi contain no microscopically demonstrable crystals. Those laminations which support a layer of crystals appear to lie in the center of the layer with equal quantities of crystal on each surface of the membrane (fig. 2, *E* and *F*). The crystals which accompany any given lamination are uniformly distributed along the lamination in all directions, as shown by serial sections. The quantity of crystal in any given volume of a calculus is invariably directly proportional to the number of laminations within the chosen area. Stated conversely, the crystal concentration in the cross section of any calculus is always greatest where the crystal-bearing laminations are in closest proximity and least concentrated where the laminations are most widely separated.

[8] Boyce, W. H., Pool, C. S., Meschan, I. and King, J. S.: Microradiographic comparison of crystalline structure with microscopic and histochemical studies of the organic matrix of urinary calculi. (Accepted for publication in Acta Radiol.)

[9] Lagergren, C.: Biophysical investigations of urinary calculi; an x-ray crystallographic and microradiographic study. Acta Radiol. (Suppl.), **133:** 1–71, 1956.

TABLE 1. *Comparable analyses of decrystallized matrix from pools of calculi and untreated uromucoid from normal urine*

	Calcigerous Calculi	"Matrix" Calculi	Uric Acid Calculi	Uromucoid
% Matrix in original calculi (dry weights)	3.2	65.0	2.2	
Inorganic ash (remaining after complete decrystallization)				
% Ash in matrix	13.1	17.6	14.2	4.8
% Ca in ash	28.7	6.1	22.4	7.1
% P in ash	13.0	9.8	1.5	21.3
Organic				
Protein (N × 6.25)	63.4	67.8	76.3	64.7
Hexose (glucide)	9.6	8.9	5.9	10.7
Hexosamine	4.9	1.5	1.5	5.2
"Sialic acid"				3.5
Bound water	10.9	12.7	10.2	6.3

Ash determined after decrystallization in EDTA, dialysis against distilled water, and lyophilization. Uric acid calculi contained 34.2% ash after removal of all uric acid and before treatment in EDTA.

Hexose—Mean values from orcinol and anthrone methods. These are only approximate since standards of glucose-mannose are not strictly comparable in color development to the mixtures of galactose, glucose, mannose, fucose and rhamnose present in the test samples.

Some calcigerous calculi contain no more hexosamine than the "matrix" and uric acid calculi.

MATRIX AS A DETERMINANT OF CRYSTAL COMPOSITION

The morphology of the matrix determines not only the position but, to a large extent, the chemical composition of the crystalline content of a calculus.

Apatite occurs only in close proximity to laminar matrix. The matrix of pure apatite calculi is invariably composed of fine laminations of matrix in uniformly contiguous alignment.

Magnesium ammonium phosphate has shown no alignment with laminar matrix but invariably occurs in amorphous matrix. No calculus with either a uniformly amorphous matrix or a pure magnesium ammonium phosphate crystalline composition has been observed.

Uric acid and calcium oxalate monohydrate appear to have a predilection for laminar matrix. Both of these crystal types also occur in amorphous matrix between laminations. Pure calculi of either type form the most uniformly crystallized stones yet observed with crystals joining contiguous laminations.

Calcium oxalate dihydrate shows no predilection for laminar matrix, but usually appears in the interlaminar areas. Growth of these crystals to large size may impinge upon and distort surrounding laminations. In many instances masses of these crystals appear to have formed as localized surface deposits which were subsequently covered by additional matrix. The formation of laminations and deposition of other crystal types resulted in entrapment of the calcium oxalate dihydrate as localized deposits within the body of the calculus (fig. 6, *B*).

MATRIX AS A DETERMINANT OF GROSS STRUCTURE

The fundamental morphology observed in the poorly crystallized matrix calculi is invariably present in fully crystallized calculi. The uniformity of the laminar structure is least distorted in pure apatite and pure uric acid calculi. This structure is often well preserved in pure calcium oxalate monohydrate renal calculi and in single large vesical calculi. The greatest distortion of basic laminar structure appears in large branched ("staghorn") calculi containing magnesium ammonium phosphate and in spinous calculi ("jackstones") of calcium oxalate monohydrate.

Figure 3 illustrates three serial sections from various parts of a typical "jackstone." The central body of the calculus is formed of uniform concentric laminations. The uncrystallized "core" of each spine is filled with amorphous matrix, but the surface is covered by concentric laminations which may be traced completely around each spine and the body of the calculus. A logical explanation of this structure is found in the postulation of a thick layer of amorphous mucoid deposited secondarily on the symmetrical body. As the randomly distributed molecules of mucoid became aligned into fibrils, "shrinkage" of the mass aligned some fibrils into compact membranes, which tend to form layers on the body of the calculus. The unorganized mucoid forms a

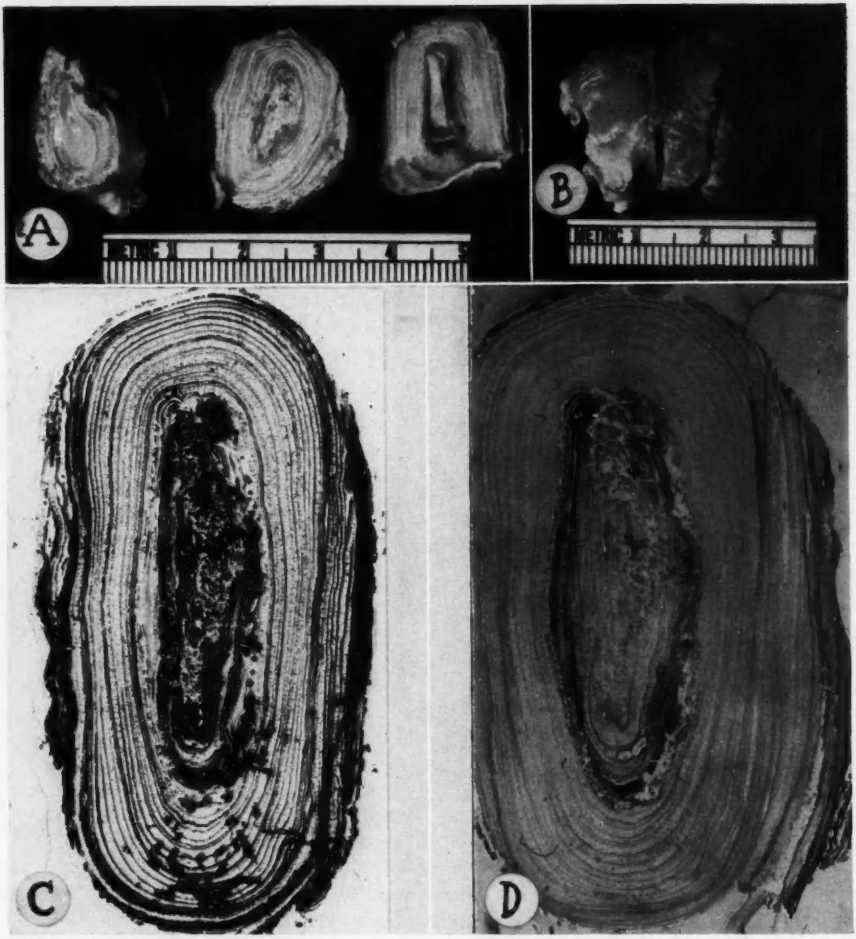

FIG. 2. Photograph of large "matrix" calculus. *A*, sectioned. *B*, reassembled to show planes of sectioning. *C*, section (8 mu.) treated by von Kossa technique to demonstrate black areas of calcium phosphate (apatite) deposition. *D*, matrix remaining after decrystallization of section *C*, aqueous toluidine blue-O treated. (See p. 107 for *E* and *F*; p. 107 for *G* and *H*.)

bulky fulcrum over which the plastic laminations are buckled by the retractive forces of orienting molecules of mucoid. These masses thus form the uncrystallized core of the spines. It is quite possible for both central body and spines of such a stone to form from a single mass of unorganized mucoid.

The structure of large branched "staghorn" calculi is illustrated in figures 4 and 5. Apatite is found only along the fine laminations, although these may not be completely crystallized in every calculus. The laminations are usually widely separated by amorphous matrix which contains magnesium ammonium phosphate or other crystals. Triple phosphate crystals are never aligned with the laminar matrix, even when these laminations are surrounded by masses of triple phosphate.

The fine laminations and dense crystalline structure of calcium oxalate monohydrate calculi are depicted in figure 6. The failure of amorphous matrix to crystallize in this type of calculus is clearly illustrated.

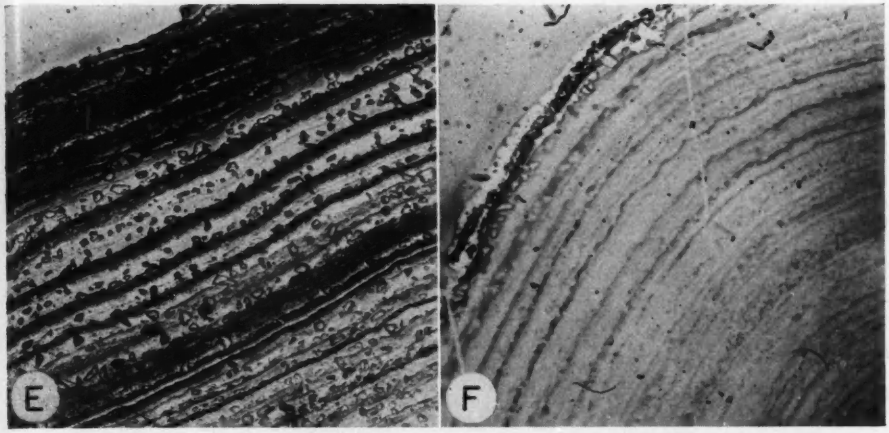

FIG. 2 (continued). (See p. 106 for *A*, *B*, *C*, *D*.) *E*, photomicrograph (147×) of marginal section of figure 2, *C*. Note dense black areas of apatite deposited along laminar matrix. Large crystals of magnesium ammonium phosphate are in random distribution within the interlaminar amorphous matrix. *F*, photomicrograph (147×) of marginal section of figure 2, *D* to demonstrate structure of decrystallized matrix. (See below for *G* and *H*.)

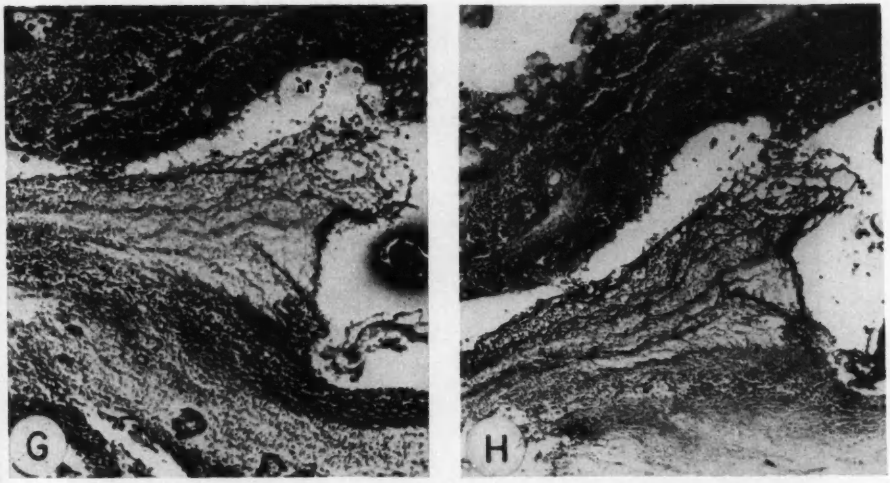

FIG. 2 (concluded). (See p. 106 for *A*, *B*, *C*, *D*; above for *E*, *F*.) *G*, photomicrograph from center of figure 2, *C* (200×) to demonstrate position of apatite (black) in unoriented fibrillar matrix. *H*, same section as figure 2, *G* after decrystallization and treatment with aqueous toluidine blue. Apatite was deposited along fibrils regardless of their configuration or relationship to adjacent fibrils.

MATRIX AS A FACTOR IN RECRYSTALLIZATION OF FORMED CALCULI

Diurnal variations in urinary pH and osmolar concentrations suggest *a priori* that recrystallization and even spontaneous decrystallization of calculi may occur. The demonstration that any of the various types of crystals of pure calcium phosphate in urine should spontaneously recrystallize to hydroxyapatite at pH 7.4[10] may be utilized to explain why hydroxyapatite is the most common constituent of urinary calculi.[9]

[10] Neuman, W. F. and Neuman, M. W.: The Mineral Phase, in The Chemical Dynamics of Bone Mineral. Chicago: The University of Chicago Press, 1958, p. 39.

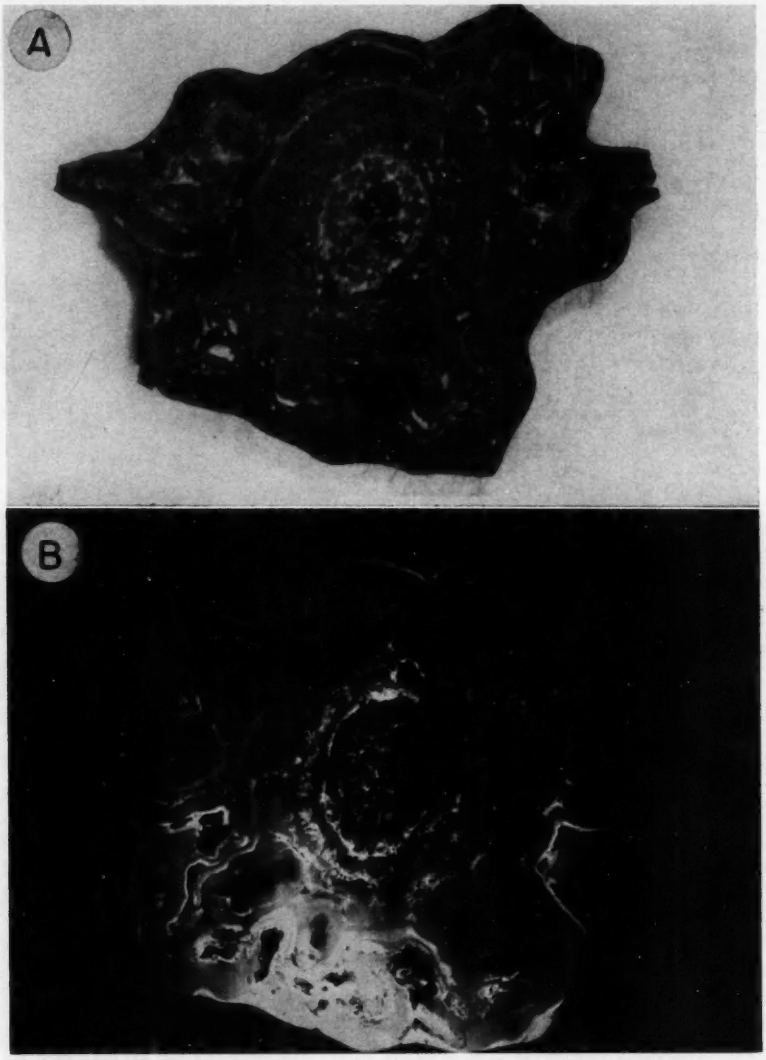

FIG. 3. Typical "jackstone". *A*, photograph of section through center of calculus. Central body is composed of concentric laminations about an irregular "core." *B*, microradiograph of *A*. Roentgenolucent areas contain amorphous matrix of minimal crystalline content. Calcium oxalate monohydrate is uniformly deposited in concentric laminations. Narrow bands of maximal roentgenopacity are apatite in fibrous matrix. (See p. 109 for *C* and *D*; p. 110 for *E* and *F*.)

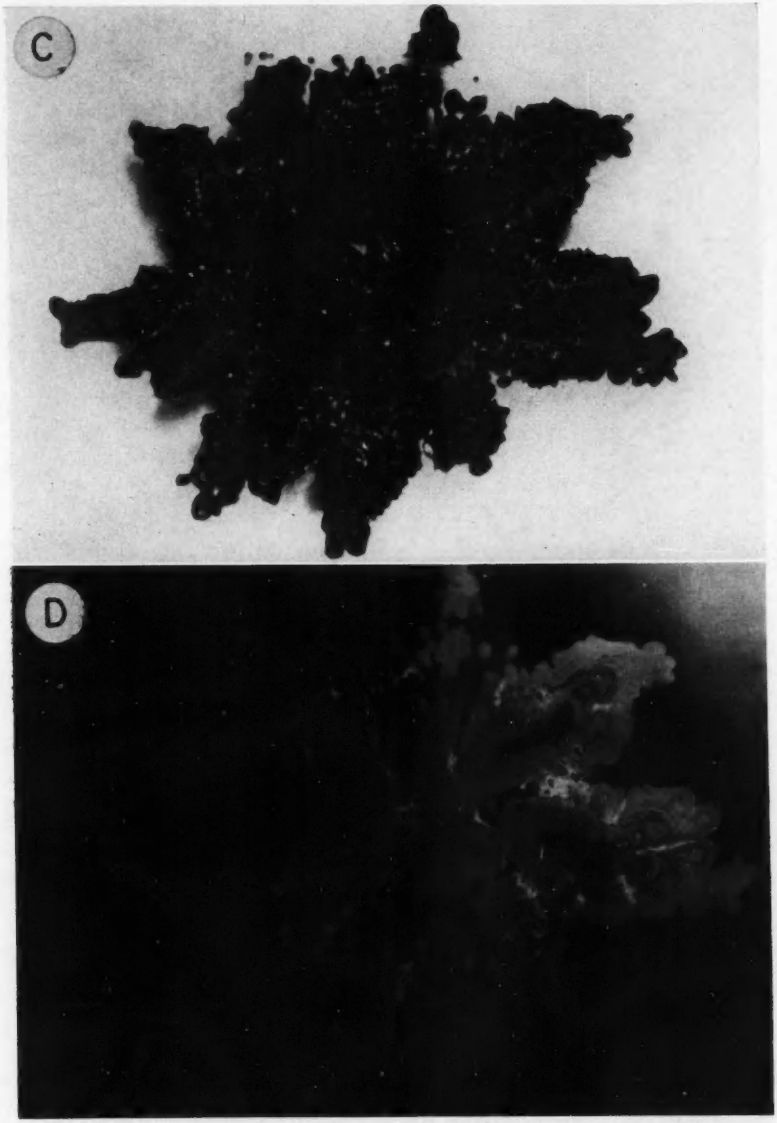

FIG. 3 (continued). (See p. 108 for *A* and *B*.) *C*, photograph of paramedian section of same calculus. Plane of section is along linear axis of several fronds. *D*, microradiograph of figure 3, *C*. Calcium oxalate monohydrate is densely deposited in fibrous laminations which parallel the long axis of each frond. Poorly mineralized core of each frond is filled with amorphous matrix. (See p. 110 for *E* and *F*.)

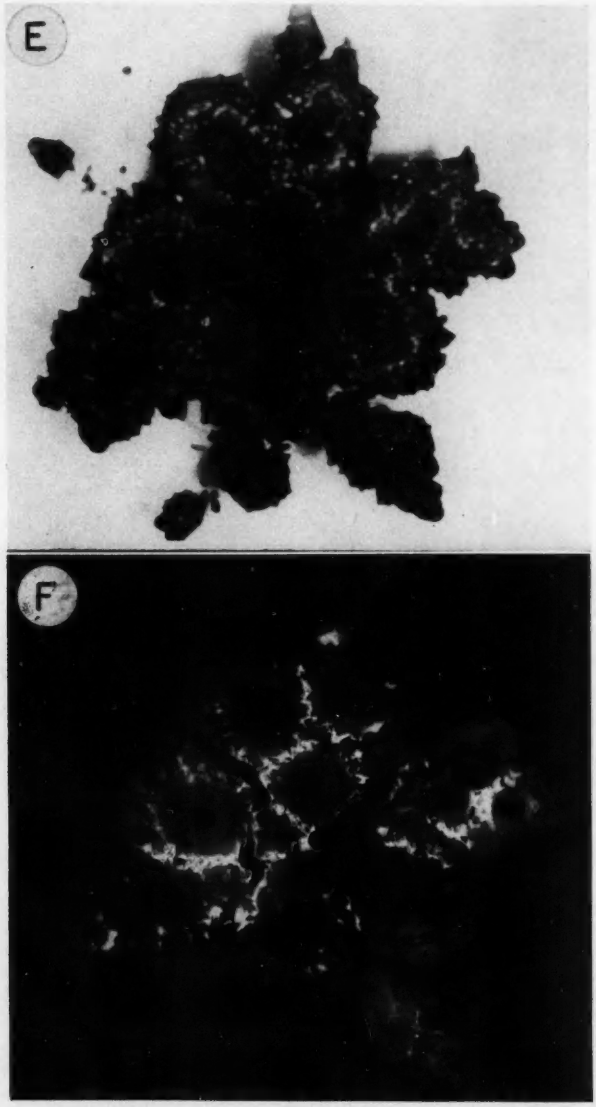

FIG. 3 (concluded). (See p. 108 for *A*, *B*; p. 109 for *C* and *D*.) *E*, marginal section of same calculus. Plane of section is at right angles to the long axis of most fronds. *F*, microradiograph of figure 3, *E*. Roentgenolucent "core" of each frond is amorphous matrix surrounded by concentric laminations of fibrous matrix which contain dense calcium oxalate monohydrate. Areas of maximal roentgenopacity are apatite in fibrous matrix.

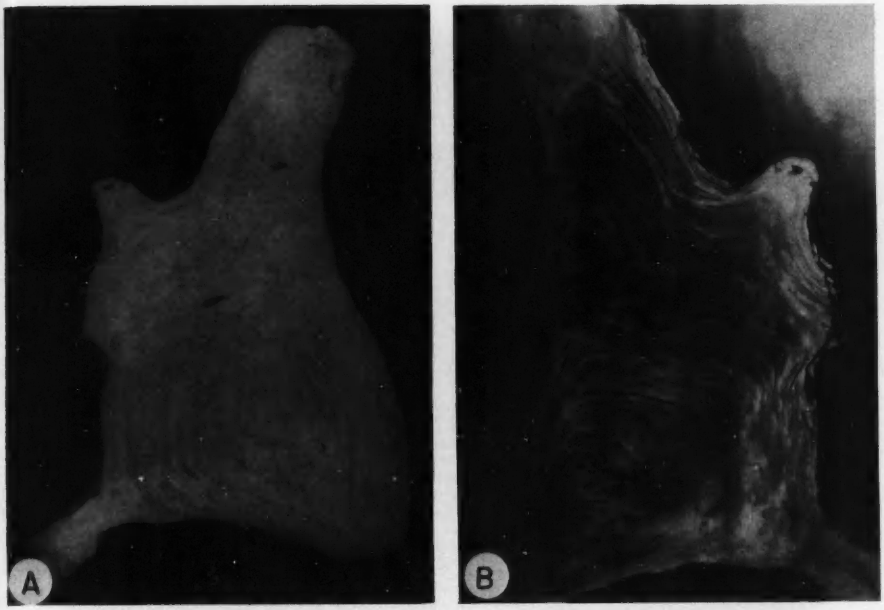

FIG. 4. *A*, photograph of median section parallel to long axis of "staghorn" calculus. Note apparent uniformity of crystal deposition. *B*, microradiograph of *A*. Highly roentgenopaque apatite is deposited along fine laminations of matrix. Less roentgenopaque magnesium ammonium phosphate appears in amorphous matrix. Observations during decrystallization indicated that many fibrous laminations contained little or no apatite, but there was no tendency for MAPH to align with these uncrystallized laminations.

Diffusion of ions into large intact calculi is readily demonstrated by immersion in dilute solutions of toluidine blue. The clinical observation that calculi rarely decrystallize must be related to some selectivity imposed on ion migration. This selectivity may well be exercised by the laminar matrix, by the amorphous matrix which uniformly fills the large interstices of crystal structure, or by both.

Figure 7 represents a crystalline structure which indicates that recrystallization may occur in calculi and may be influenced by the matrix. The dumb-bell appearance of this specimen is apparently the result of fusion of two calculi into a single stone within the renal pelvis. The center of each original calculus is composed of an aggregate of calcium oxalate dihydrate crystals. Surrounding this is less compact calcium oxalate which extends from the center to the surface. A small amount of calcium oxalate monohydrate is present in this area. The long needle crystals on the outer layers of the two original calculi are calcium hydrogen phosphate dihydrate.

The distribution of the calcium hydrogen phosphate needles is of especial interest with respect to the question of recrystallization in formed calculi. These crystals are limited to those portions of laminations 1 to 5 which are in close apposition to the surface of the original calculi. Several observations suggest that these crystals formed from Ca^{++} and $(PO_4)^{---}$ ions which were in migration *from* the centers of the original calculus *toward* the surface of the stone. First, the crystal growth spread fan-shape with the broad fan toward the surface of the calculus (fig. 7, *B*). A single crystal forms the "handle" of the fan and is located nearest the center of the calculus. Such a branched arrangement of crystals commonly forms from an initial "seed" crystal with daughter crystals forming the divergent fronds. Second, these crystals more

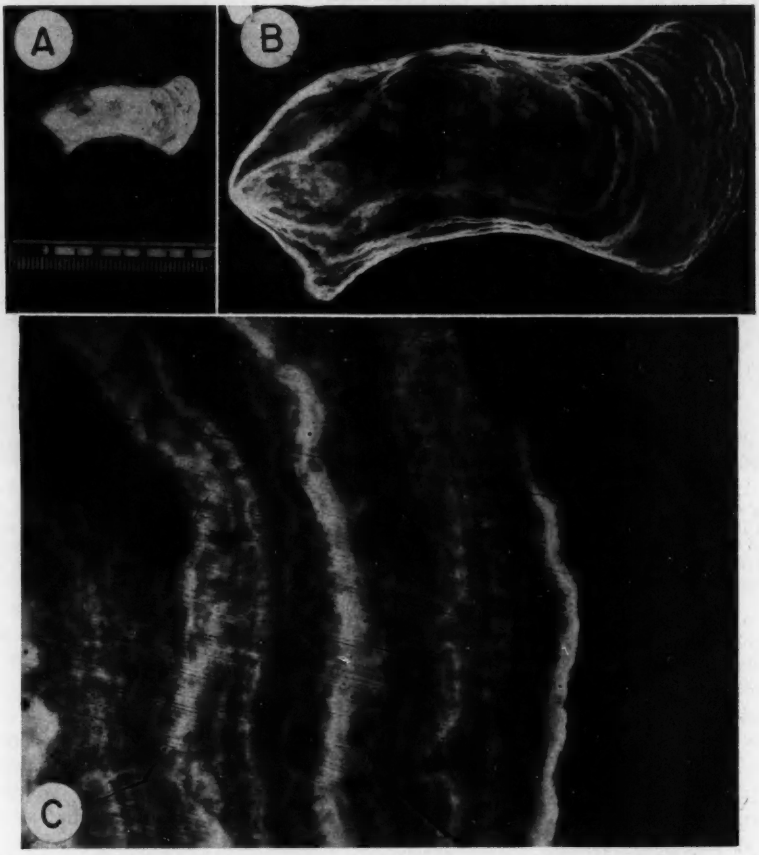

FIG. 5. *A*, photograph of section parallel to short axis of "staghorn" calculus. *B*, microradiograph of *A* illustrates dense apatite along many of fibrous laminations and variations in density of magnesium ammonium phosphate in amorphous matrix. *C*, microradiograph of margin of *A*. Apatite is deposited only on laminations and fibrils which appear between some laminations. Amorphous matrix contains magnesium ammonium phosphate. Roentgenolucent areas are filled with amorphous matrix containing a minimal amount of magnesium ammonium phosphate. (See p. 113 for *D* and *E*.)

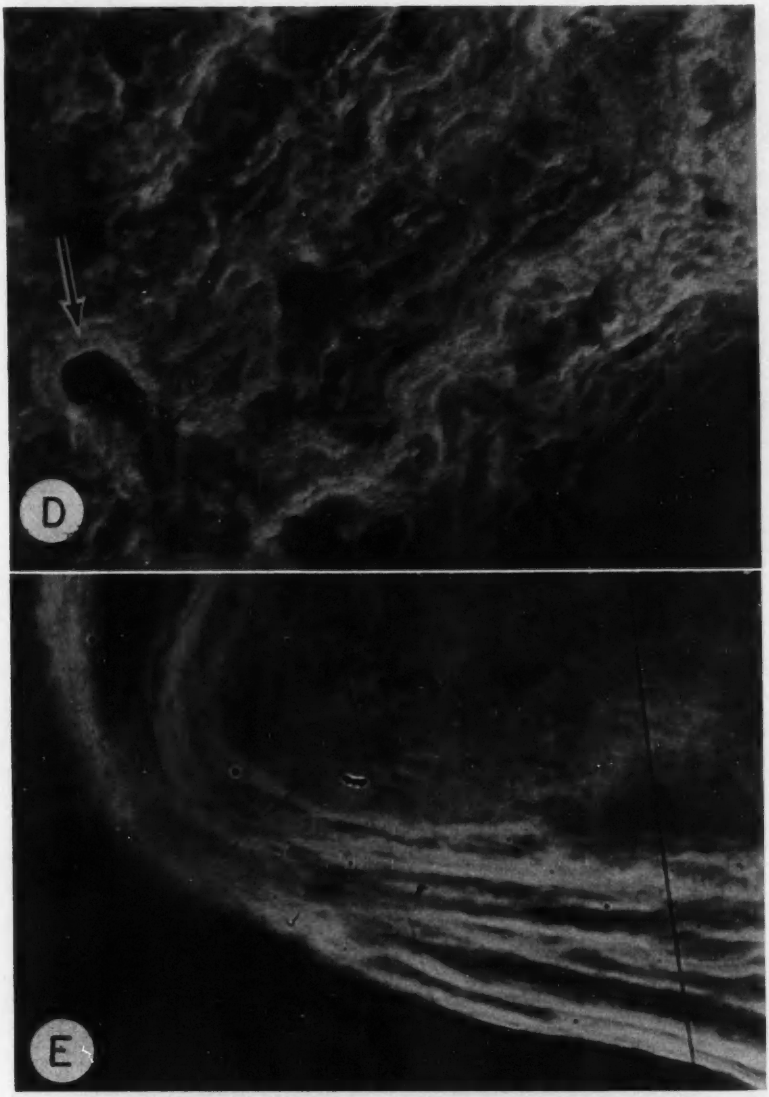

FIG. 5 (concluded). (See p. 112 for *A*, *B*, *C*.) *D*, microradiograph of margin of figure 5, *A*. Crystals are magnesium ammonium phosphate with only traces of apatite in some of fibrils. "Pores" of 100 to 500 mu. in diameter which contain neither crystals nor matrix are common in such calculi and may have extensive ramifications through body of calculus. Large "pore" (arrow) is 300 mu. in diameter. *E*, microradiograph of margin of figure 5, *A*. Apatite deposition coincides with laminations of matrix. Where laminations are in close proximity, apatite is almost uniform in deposition.

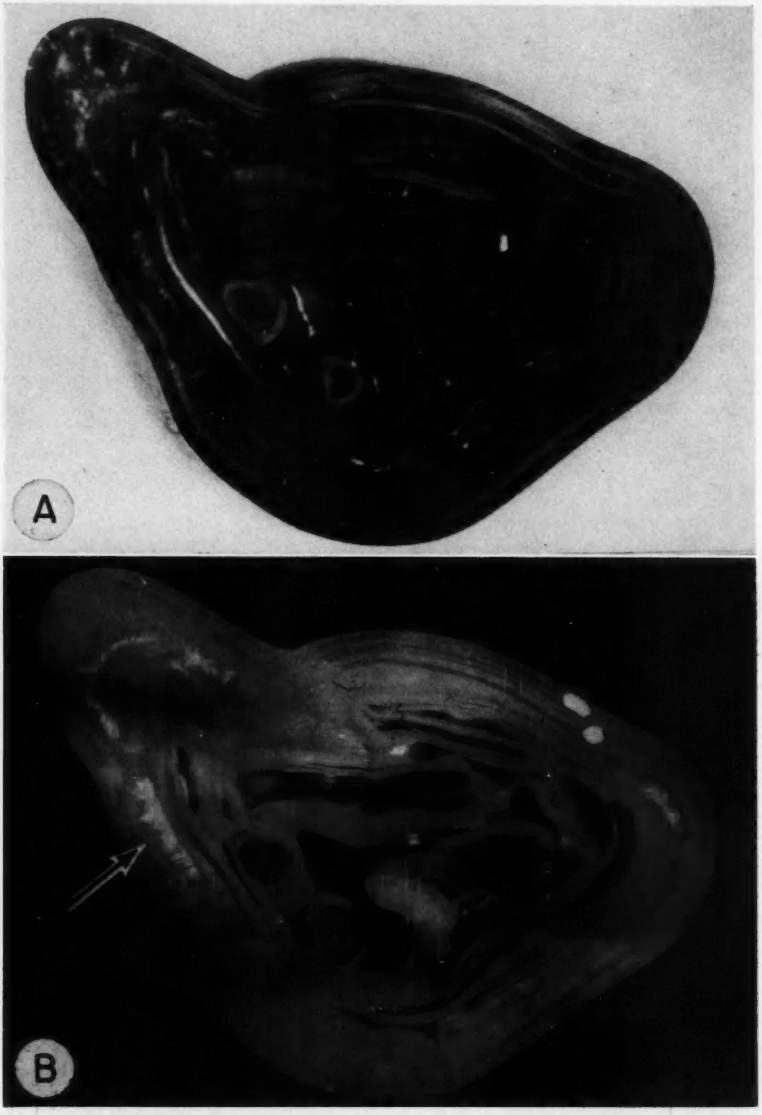

FIG. 6. *A*, photograph of median section of calcium oxalate monohydrate calculus. Crystallization appears to be of uniform density. *B*, microradiograph of *A*. Roentgenolucent areas contain amorphous matrix with few laminations or fibrils. Calcium oxalate monohydrate is uniformly deposited in the closely apposed concentric laminations. Calcium oxalate dihydrate (arrow) may have been deposited as surface crystallization which was subsequently covered by addition of matrix and calcium oxalate monohydrate. (See p. 115 for *C*.)

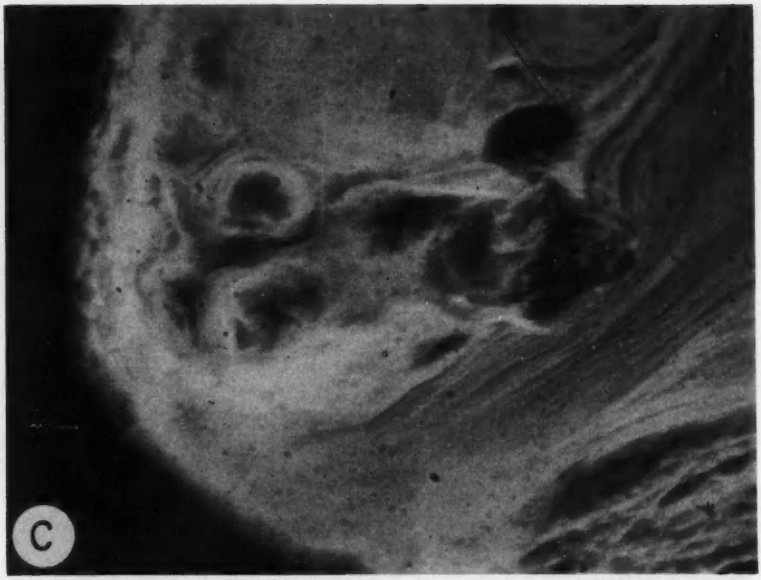

FIG. 6 (concluded). (See p. 114 for *A* and *B*.) *C*, microradiograph of projection from near center of calcium oxalate monohydrate calculus. Configuration and density of crystal deposition are clearly related to variations in matrix structure.

nearly surround the center of the original calculus in the more central laminations than in the peripheral laminations of the "secondary stone."

This arrangement could easily have developed if the two original calculi were composed of a mixture of calcium oxalate and basic calcium phosphate. A mass of mucoid was then deposited forming the matrix which joined the calculi and from which laminations 1, 2, 3, and 4 developed. A persistently acid urine permeating the newly formed matrix should result in the preferential solution of basic calcium phosphate. This situation would inevitably result in a pH and osmotic gradient between the center and surface of the calculus with the forces acting to move calcium and phosphate ions from the center to the surface of the calculi. These ions, encountering uncrystallized matrix in the peripheral laminations, were then recrystallized in the acid medium as calcium hydrogen phosphate. Failure of these crystals to form in the matrix which joined the two stones is likely due to the absence of as strong a diffusion gradient in this direction as existed in the more fibrous matrix near the surface of the original calculi where laminations 1 to 5 are in close proximity. It has been observed above that masses of amorphous matrix are poorly crystallized by any but MAPH crystals. Diffusion of ions into the more amorphous matrix joining the calculi may thus be more limited than through the closely apposed laminar matrix.

The structure also suggests that the calcium oxalate in the matrix joining the two calculi is derived not only from the urine but by erosion from the contiguous borders of the original calculi.

Regardless of the interpretation one may place on the position of the crystals in these microradiographs, the architectonic function of the organic matrix is self-evident.

SUMMARY

The fundamental morphology of all calculi is a system of concentric laminations of fibrous matrix, with a variable quantity of interlaminar amorphous matrix. Calculi with matrices of purely laminar form (pure apatite) have been observed but no calculus with a completely amorphous matrix has been seen.

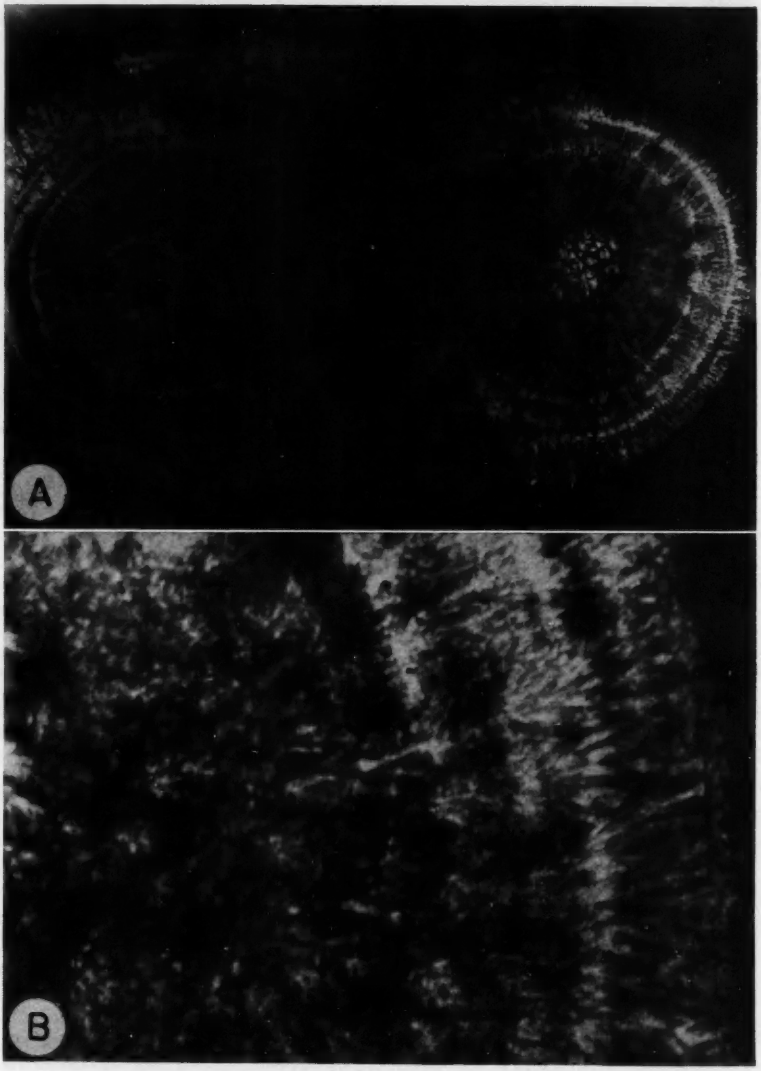

FIG. 7. *A*, microradiograph of specimen formed by union of two smaller calculi. Central area of each original calculus contains calcium oxalate dihydrate. Most commonly distributed crystals are sparsely arranged calcium oxalate monohydrate. Needle-shaped crystals in fan-line patterns are calcium hydrogen phosphate monohydrate. Enlarged 5×. *B*, marginal microradiograph of *A*, enlarged 20×.

Evidence has been presented that matrix is a determining factor in the position and composition of crystal deposits in calculi. The influence of ambient urinary conditions on crystal structure and concentration is not negated by this concept. However, these observations support the thesis that no concretion is ever formed as a sedimentary mass of crystals, since the architectural structure of calculi can only result from deposition of crystals upon or within a preformed matrix. The presence of a crystallizable matrix is thus the essential factor and the initial phase in concrement formation.

The authors wish to acknowledge the valuable contributions of the following individuals to this study:

Microradiography by Dr. Chalmers S. Pool, Department of Radiology, Veterans Administration Hospital, Little Rock, Arkansas.

Instruction in the use of the petrographic microscope for crystal identification by Dr. Virgil I. Mann, associate professor of geology, the University of North Carolina, Chapel Hill, North Carolina.

Histochemical studies by Dr. Norman M. Sulkin, professor of anatomy, The Bowman Gray School of Medicine.

Electron microscopy of selected specimens by Dr. Robert A. Robinson, professor of orthopedics, Johns Hopkins Hospital, Baltimore 5, Maryland.

THE INFLUENCE OF CORTISONE AND THYROID EXTRACT ON POST-HYPOPHYSECTOMY DISSOLUTION OF EXPERIMENTAL VESICAL CALCULI IN RATS

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It seems amply confirmed that adrenocortical atrophy occurs in many species after complete hypophysectomy.[1-4] Lipsett, West, MacLean and Pearson, in studies of patients with metastatic cancer who had had surgical hypophysectomy, observed adrenal insufficiency[5] and hypothyroidism[6] in all. Luft, Olivecrona and Sjogren also noted thyroid hypofunction in their hypophysectomized patients. Evaluation of adrenocortical function was difficult because of the need for cortisone treatment for prolonged periods of time.[7] In the postoperative medical management of hypophysectomized patients, cortisone and thyroid replacement therapy is imperative[8] to obviate secondary adrenocortical insufficiency and myxedema, which inevitably ensues. Numerous studies have shown that adrenocortical hormones suppress thyroid gland function.[6, 9, 10-14]

In a previous experiment,[15] we found that when Long-Evans male rats bearing experimental vesical calculi were subjected to hypophysectomy, ninety-seven per cent dissolved an average of 79 per cent of the stone in four weeks. Because we have also found that cortisone treatment in the intact rat stimulates calculogenesis,[16] the present study was conducted to find out if cortisone and thyroid administration would reduce the therapeutic effectiveness of hypophysectomy.

MATERIALS AND METHODS

The urinary bladders of Long-Evans male rats, weighing 125–175 gm., were aseptically implanted with 15 mg. magnesium pellets. Rats were given Purina laboratory chow and tap water ad libitum. Four weeks after the implantation of the magnesium ribbon nidus, the bladders were re-opened. The primary stones were weighed on a Gramatic balance and replaced in the urinary bladder after all secondary, or daughter stones were removed and discarded. The urine pH was taken with short range test

[1] Smith, P. E.: Hypophysectomy and replacement therapy in the rat. Am. J. Anat., **45:** 205, 1930.

[2] Houssay, B. A., Biasotti, A., Mazzoco, P. and Sammartino, R.: Action of the extract of anterior hypophysis on suprarenals. Compt. Rend. Soc. de Biol., **114:** 737, 1933.

[3] Collip, J. B., Anderson, E. M. and Thomson, D. L.: Adrenotropic hormone of anterior pituitary lobe. Lancet, **2:** 347, 1933.

[4] Shumacker, H. B. and Firor, W. M.: Interrelationship of adrenal cortex and anterior lobe of hypophysis. Endocrinology, **18:** 676, 1934.

[5] Lipsett, M. B., West, C. D., MacLean, J. P. and Pearson, O. H.: Adrenal function after hypophysectomy in man. J. Clin. Endocrinol. & Metab., **17:** 356, 1957.

[6] Li, M. C., Rall, J. E., MacLean, J. P., Lipsett, M. B., Ray, B. S. and Pearson, O. H.: Thyroid function following hypophysectomy in man. J. Clin. Endocrinol. & Metab., **15:** 1228, 1955.

[7] Luft, R., Olivecrona, H. and Sjogren, B.: Hypophysectomy in man: Experiences in severe diabetes mellitus. J. Clin. Endocrinol. & Metab., **15:** 391, 1955.

[8] Lipsett, M. B., Li, M. C. and Pearson, O. H.: Medical management of adrenalectomy and hypophysectomy. Arch. Int. Med., **96:** 634, 1956.

[9] Hill, S. T., Reiss, R. S., Forsham, P. H. and Thorn, G. W.: The effect of adrenocorticotropin and cortisone on thyroid function; thyroid-adrenocortical interrelationships. J. Clin. Endocrinol., **10:** 1363, 1950.

[10] Kuhl, W. J., Jr. and Ziff, M.: Alteration of thyroid function by ACTH and cortisone. J. Clin. Endocrinol. & Metab., **12:** 554, 1952.

[11] Fredrickson, D. S., Forsham, P. H. and Thorn, G. W.: The effect of massive cortisone therapy on measurements of thyroid function. J. Clin. Endocrinol. & Metab., **12:** 541, 1952.

[12] Goldenburg, I. S., Lutwak, L., Rosenbaum, P. J. and Hayes, M. A.: Thyroidadrenocortical interrelations following operation. Surg., Gynec. & Obst., **98:** 513, 1954.

[13] Goldenburg, I. S., Lutwak, L., Rosenbaum, P. J. and Hayes, M. A.: Thyroidadrenocortical metabolic interrelations. J. Clin. Endocrinol. & Metab., **15:** 227, 1955.

[14] Sherer, M. G. and Siefring, B. N.: Effect of prednisone and prednisolone on thyroid function, with special reference to thyroxine-binding protein in nephrosis. J. Clin. Endocrinol. & Metab., **16:** 643, 1956.

[15] McDonald, D. F. and Orallo, M. O.: Dissolution of experimental vesical calculi by hypophysectomy in rats. Endocrinology, **63:** 132, 1958.

[16] McDonald, D. F.: Cortisone and Calculus, Urologists Letter Club, April 3, 1956.

TABLE 1. *The effect of cortisone-thyroid therapy on calculogenesis in hypophysectomized rats*

Group	No. of Rats	Calculus Change			24 Hr. Fluid Intake/Rat	P Value (Fluid Intake)
		% ± group	Mg ± Calculus	% ± Calculus		
					ml.	
1. Control*	19	+100	+139	+164	51.8	
2. Sham-hypophysectomized*	9	+100	+142	+160	54.1	<.2
3. Hypophysectomized	15	−100	−85	−83	45.0	<.05
4. Hypophysectomized*	15	−93	−76	−75	41.4	<.001
		+7	+6	+3		

* Injected daily with cortisone acetate 0.5 mg./kg. and U.S.P. thyroid powder 0.4 mg./kg.

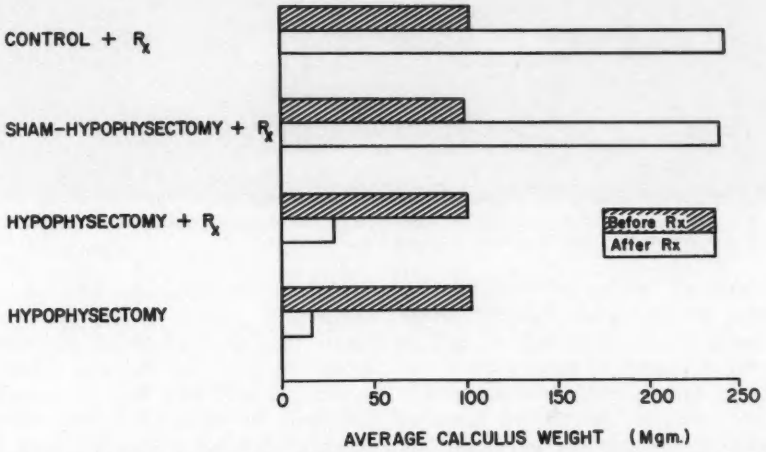

FIG. 1. Variation in size of experimental bladder calculi before and after hypophysectomy and treatment with cortisone and thyroid extract.

paper and initial body weights were noted. Hypophysectomy and sham-hypophysectomy were performed two days after the stones were reinserted in the urinary bladders.* Treatment with cortisone acetate and thyroid extract was started nine days after hypophysectomy. Each group consisted of ten to twenty rats: One group of hypophysectomized animals and the sham-hypophysectomized rats received cortisone acetate, Merck, 0.5 mg./kg., intramuscularly, and U.S.P. thyroid powder, Armour, 0.4 mg./kg., intraperitoneally, daily for four consecutive weeks. The other group of hypophysectomized rats received no treatment. Weekly body weights were recorded. All rats were kept in a warm room, from 80–82F. The 24 hour fluid intake was measured for each group during the course of treatment. Statistical analysis was done according to Fisher. The probability was taken from his table.[17]

* At the Diablo Animal Laboratories, San Francisco, California.

RESULTS

Four weeks after magnesium pellet implantation, all the animals except one developed vesical calculi varying from 26 mg. to 267 mg. The average primary calculus weight at the time the stones were re-implanted was 121.6 mg.

Table 1 tabulates the results after four weeks of treatment. All treated control rats and treated sham-hypophysectomized animals had a marked increase in stone size. Most of them had daughter stones. None of the thirty hypophysectomized animals had daughter stones. All of the stones

[17] Fisher, R. A.: Statistical Methods for Research Workers. Edinburgh: Oliver and Boyd, Ltd., 1948.

FIG. 2. Variation in size of experimental bladder calculi in sham-hypophysectomized and hypophysectomized rats following treatment with cortisone and thyroid.

in the untreated hypophysectomized group decreased an average of 83.4 per cent of the initial primary stone weight; one rat had no stone at the conclusion of the treatment. All but one of the animals, and it was incompletely hypophysectomized, in the treated hypophysectomized group lost an average of 74.9 per cent of the initial calculus weight. These results are graphically shown in figure 1. The untreated hypophysectomized animals lost an average of 18.3 per cent of their initial body weight; the treated hypophysectomized animals lost 20.7 per cent.

The control and sham-hypophysectomized animals had significantly greater average 24 hour fluid intake than the hypophysectomized animals. One sham-hypophysectomized rat died before completion of treatment. There were no deaths in the other groups.

Statistical evaluation of the results showed highly significant ($P < .001$) increases in stone weight in the control and sham-hypophysectomized groups and decreases in stone weight in both hypophysectomized groups. The difference between the controls and the sham-hypophysectomized treated rats was not significant ($P < .9$). The difference between the untreated hypophysectomized and the treated group was not significant ($P < .2$). The controls had significantly greater twenty-four hour fluid intake than the untreated hypophysectomized group ($P < .05$) and the treated hypophysectomized group (P .001). There were no significant differences in water intake between the two hypophysectomized groups ($P < .3$) and between the controls and the sham-hypophysectomized animals (P .2).

DISCUSSION

The reduction in the urinary excretion of calcium, magnesium and phosphorus following hypophysectomy diminishes the tendency to form urinary concrements. The exact mechanism involved in the dissolution of experimental vesical calculi in rats after hypophysectomy is not known. Changes in electrolytes possibly play an important role. No electrolyte determinations were done in the present study. A fall in the urinary inorganic phosphorus excretion following the administration of hydrocortisone was demonstrated by Persky and co-workers.[18]

[18] Persky, M., Linsk, J., Isaacs, M., Jenkins, J. P., Rosenbluth, M. and Kupperman, H. S.: Acute effects of intravenous hydrocortisone on glucose and insulin tolerances, and levels of serum and urinary inorganic phosphorus. J. Clin. Endocrinol. & Metab., **15**: 1247, 1955.

This means there is less phosphate available to combine with calcium and/or magnesium. It is noted that none of the hypophysectomized animals developed secondary or daughter stones, whereas, most of the controls and the sham-hypophysectomized rats had secondary stones. Since there was no statistical significance to slight differences in size of calculi in treated and untreated groups of hypophysectomized animals, the effect of stress was either negligible or was abolished by the action of administered medicaments. The differences in 24 hour fluid intake cannot be explained at present. The daily urine output per rat was not measured, but polyuria could not have been present, since there was a significantly lower 24 hour fluid intake in the hypophysectomized animals.

The possible usefulness of adrenocortical steroids (corticotrophin or phenylbutazone) in reducing incidence of recurrent calculi has been suggested by Baker and Connelly.[19] But McDonald[20] has reported that cortisone administration to intact male rats bearing experimental vesical calculi triples the rate of formation of stone. Baker and Connelly consider urolithiasis a disease of renal connective tissue matrix. If so, perhaps cortisone could exert an anti-inflammatory effect. After prolonged administration of cortisone to hypophysectomized rats, Greenberg and Aterman were unable to demonstrate significant androgenic activity of cortisone.[21] We have observed that testosterone (androgen) administration to male hypophysectomized rats promotes calculus formation.[20]

[19] Baker, R. and Connelly, J. P.: Bilateral and recurrent renal calculi. J.A.M.A., **160:** 1106, 1956.

[20] McDonald, D. F. and Eddings, R. A.: Influence of hypophysectomy and replacement therapy on experimentally induced calculi in rats. J. Urol., **77:** 238, 1957.

SUMMARY

Following hypophysectomy, primary experimentally-induced vesical calculi in male Long-Evans rats dissolved and the formation of secondary or daughter stones was prevented. The administration of doses of cortisone and thyroid extract comparable to those necessary to prevent clinical hypothyroidism and hypoadrenocorticism in humans does not abolish the influence of hypophysectomy in dissolution of pre-formed calculi. Hypophysectomy, as a therapeutic modality in advanced urolithiasis, may, therefore, be practical, as well as effective.

[21] Greenberg, S. M. and Aterman, K.: Effects of prolonged cortisone administration to hypophysectomized rats. Endocrinology, **55:** 700, 1954.

EXPERIMENTS IN UROLITHIASIS: I. HISTOCHEMICAL STUDIES

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Great emphasis is being placed lately in the possible role of mucopolysaccharides in the formation of renal calculi. Although the analysis of this angle of the problem has contributed considerably to the knowledge of the process of calcification, the basic information in this regard is nevertheless very tenuous and sometimes contradictory. It seems that one is still dealing with "peripheral factors" rather than with basic data.

Previous investigations have shown increase and alteration in mucopolysaccharides of the renal tubules in experimental urolithiasis; different working hypotheses were advanced based on these findings.[1-4] However, we could find no data concerning human renal calcification utilizing histologic stains which are selective for mucopolysaccharides; this was believed to be an approach worthwhile investigating.

METHODS

The material used in this study was obtained from 10 kidneys surgically removed and three renal biopsies in patients with nephrolithiasis of different degrees; in all cases the calculi were formed mainly by calcium salts but none of the cases had any evidence of hyperparathyroidism.

Specimens with severe and extensive pyelonephritis were discarded. The sample of tissue examined was taken as far away as possible from the pyelonephritic lesions in the specimens. All tissue was fixed in 10 per cent formalin solution.

Besides routine hematoxylin-eosin stains the specimens were subjected to two types of histochemical reactions: 1) Von Kossa stain for calcium, associated to a) PAS or orange G stain with background by light green, b) nuclear stain by Delafield hematoxylin* in material treated by saliva (15 minutes at 56°C). By these techniques we endeavored to identify the mucopolysaccharides and the calcareous deposits in adjacent specimens rather than simultaneously although the hematoxylin staining enabled, up to a certain point, simultaneous observation of mucopolysaccharides and calcium. 2) Stain with a 1 per cent solution of toluidine blue in tissue treated by hyaluronidase† (1 hour at 37°C): this metachromatic stain with enzyme treatment permits an evaluation of the depolymerization of mucopolysaccharide bound to protein.

RESULTS

In the PAS stained, saliva treated specimens the same changes reported by other investigators were observed: As compared to the normal (fig. 1), there was an increase in PAS positive material in the basement membrane of the tubules, in the brush border of the proximal convoluted tubules and, occasionally, in the hyalin droplets of the cells in the proximal tubule.

In the overwhelming majority of cases several PAS positive casts were observed within the tubules (fig. 2, *A*).

The basement membrane showed different degrees of thickening; at times it included the entire length of the membrane (fig. 2, *B*) while in others the thickening was observed only in certain parts (fig. 2, *C* and *D*). In some instances the thickening was so marked that the tubular epithelium could not be visualized although the tubular lumen was not diminished (fig. 2, *C*); in such cases the patchy thickening often appeared as nodules scattered in the inner surface of the membrane (fig. 2, *D*). Attention should be called

[1] Rubin, P. S. and Howard, J. E.: Histochemical studies in the role of acid mucopolysaccharides in calcifiability and calcification. Trans. 2nd Jos. Macy Conf. Metab., 1950.

[2] Baker, R., Reaven, G. and Sawyer, J.: Ground substance and calcification. J. Urol., **71:** 511, 1954.

[3] Baker, R. and Sison, F.: Demonstration of altered tissue mucopolysaccharides in renal calculous diseases by selective staining techniques. J. Urol., **72:** 1032, 1954.

[4] Grimes, A. W.: A phase contrast study of the mechanism of renal calcification. J. Urol., **78:** 553, 1957.

* This Delafield hematoxylin stain was undertaken because the Von Kossa did not stain calcium adequately in the specimens used; this occurrence might be due to the fact that all specimens were fixed in formaldehyde for rather prolonged periods and this led to indiscriminate precipitation of silver salts in the tissue.

In the hematoxylin stain the calcium specimens were stained in blue whereas the less densely calcified granular material stained brown.

† The authors are indebted to Schering Laboratories of Brazil for a generous supply of hironase.

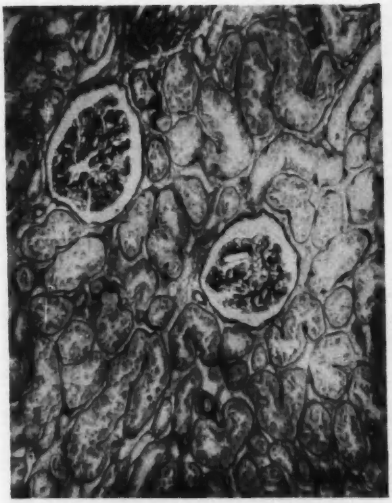

FIG. 1. PAS stain of normal renal tissue of man shows basement membrane of glomeruli and tubules (oc.8× obj.10,Leitz).

to the fact that none of the thickening mentioned here could be confused with artefacts as a bias or a tangential cut of tubules, or others.

In no instance PAS positive material could be identified in the cytoplasm of the cells. Calcium-containing material could not be identified either in the thickened basement membrane or within the cytoplasm of the cells.

In the tubular lumen, however, the existence of calcareous spheres or granular formations which were surrounded by homogeneous material PAS positive (figs. 3–6) was frequently observed.

The toluidine blue stain was used in an attempt to identify metachromatic material in the tubular lumen or in the cells; it was persistently negative and the PAS-positive casts also kept their orthochromatic stain. Likewise, the tissue treated with hyaluronidase could not show any change in the staining properties of these structures.

COMMENTS

The prevailing opinion is that chondroitin sulfates are the mucopolysaccharides which bind the proteins to form mucoproteins.[5, 6] It is also accepted that chondroitin sulfuric acid is one of the components of the basement membrane because being a PAS positive structure it stains red by the technique of Ritter and Oleson,[7] which is specific for this compound. The increase in mucopolysaccharide on the tubular basement membrane observed by Baker and Sison[3] in experimental urolithiasis, with subsequent calcification, suggests that changes of the ground substance represent the chemical basis of renal calcification. However, in the specimens examined in this work, which included a wide variety of nephrolithiasis, no calcium deposits were observed in the thickened basement membrane, although the increase of mucopolysaccharide was persistently detected.

The thickening of the basement membrane can easily be interpreted both in experimental as well as in human nephrolithiasis as the reaction to injury, identical to most irritating factors, as pointed by McManus.[8] The calcification of the basement membrane observed in experimental nephrolithiasis can also be interpreted, according to Grimes[4] as a special form of reaction to injury determined by the markedly elevated blood calcium level.

Although the histochemical reactions in renal tissue are not fully known, certain concepts of staining properties in other tissues can be applied to the kidney. Cobb[9] while studying the bone matrix found that the greater the degree of polymerization of mucoprotein the less intense is the staining reaction with PAS. On the other hand Persson[10] believes that the intensity of PAS staining is indicative of the strength of mucopolysaccharide-protein bound.

Both in experimental and in human nephrolithiasis, the casts persistently found in the tubular lumen showed a markedly positive PAS staining. Besides, in the toluidine blue staining the reaction was orthochromatic and not metachromatic, the reaction being unaltered by hyaluronidase. This confirms in humans Baker's[2]

[5] Sylven, B.: Cartilage and chondroitin sulphate. J. Bone & Joint Surg., **29**: 745, 1947.

[6] Sobel, A. E. and Burger, M.: Calcification; investigation of role of chondroitin sulfate in the calcifying mechanism. Proc. Soc. Exp. Biol. Med., **87**: 7, 1954.

[7] Ehrich, W. E.: *In* Etiologic Factors in Renal Lithiasis. Springfield, Ill.: Charles C Thomas, 1956, p. 278.

[8] McManus, J. F. A.: Medical Diseases of the Kidney. Philadelphia. Lea & Febiger, 1950.

[9] Cobb, quoted in Engel, M. B.: Mobilization of mucoprotein by parathyroid extract. Arch. Path., **53**: 339, 1952.

[10] Persson, B. H.: Studies on connective tissue ground substance. Acta Soc. Med. Ups., n.s. 58. Upsala: Almquist & Wiksell, 1953.

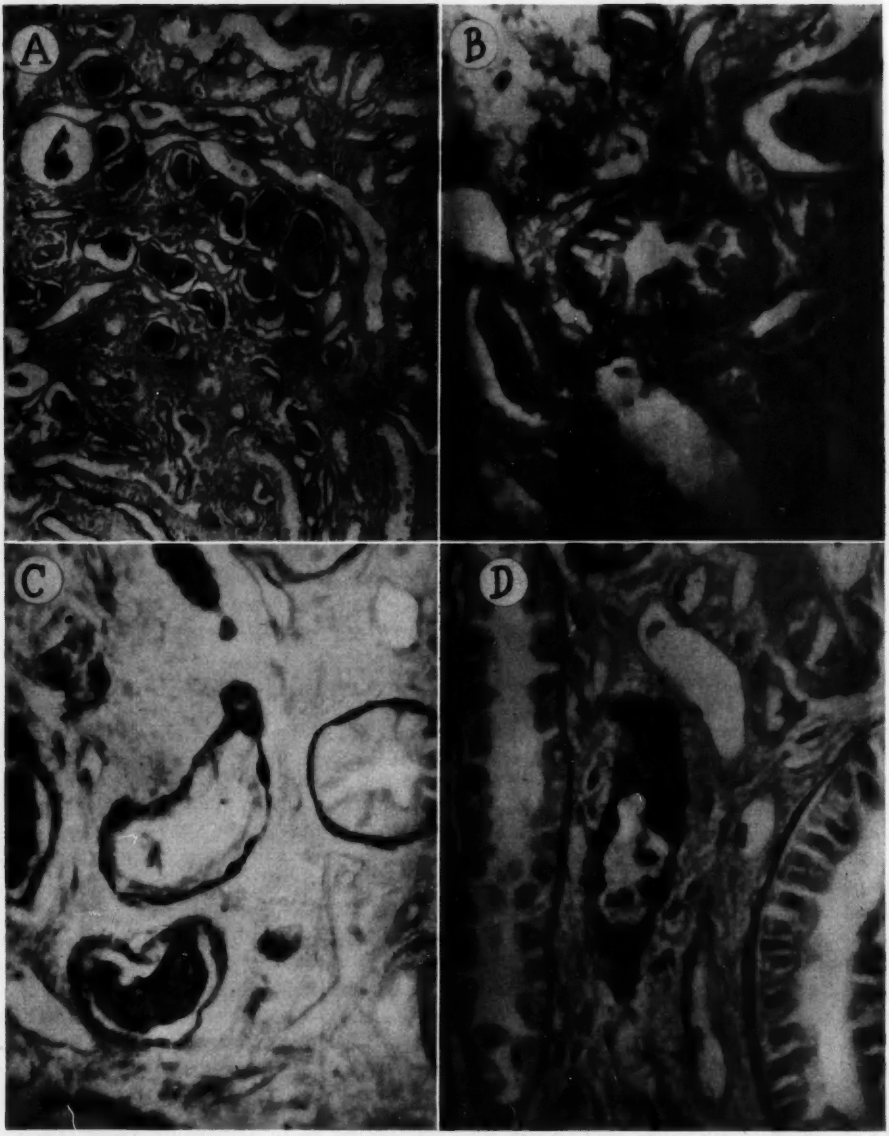

FIG. 2. *A*, PAS stain of human kidney with calculous disease shows several PAS positive casts in tubular lumen (oc.8× obj.10,Leitz). *B*, PAS stain of human kidney with calculous disease shows diffuse thickening of tubular basement membrane (oc.8× obj.45,Leitz). *C*, PAS stain of human kidney with calculous disease shows segmental thickening of basement membrane; note disappearance of cellular limits (oc.8× obj. 45,Leitz). *D*, PAS stain of human kidney with calculous disease shows segmental thickening of basement membrane with nodules of increased thickening (oc.8× obj.45,Leitz).

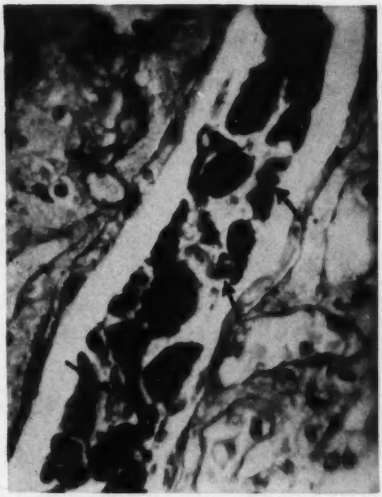

FIG. 3. PAS plus hematoxylin stain of human kidney with calculous disease shows within tubular lumen clumps of PAS positive material associated with hematoxylinophile material, probably of calcareous nature (oc.8× obj.45,Leitz).

interpretation of his findings in animals that increased mucoproteins in the tubular lumen were markedly depolymerized.

It is well accepted that depolymerized mucoproteins bind calcium more effectively than the highly polymerized compounds.[1] Observations in experimental as well as in human nephrolithiasis show a markedly positive PAS reaction, indicative of markedly depolymerized mucoprotein, therefore pointing to a compound highly capable of binding calcium. Besides, in patients with calculous disease the urine contains calcium-bound mucoproteins.[11]

However, in experimental urolithiasis no calcium was ever observed in PAS positive casts within the tubular lumen. Possibly in view of this condition as well as due to his findings of intracytoplasmic calcified granules of mucoprotein, Grimes[4] established his working hypothesis for the formation of renal calcification.

[11] Boyce, W. H., Garvey, F. K. and Norfleet, C. M.: Proteins and other biocolloids of urine in health and disease. J. Clin. Invest., **33:** 1287, 1954.

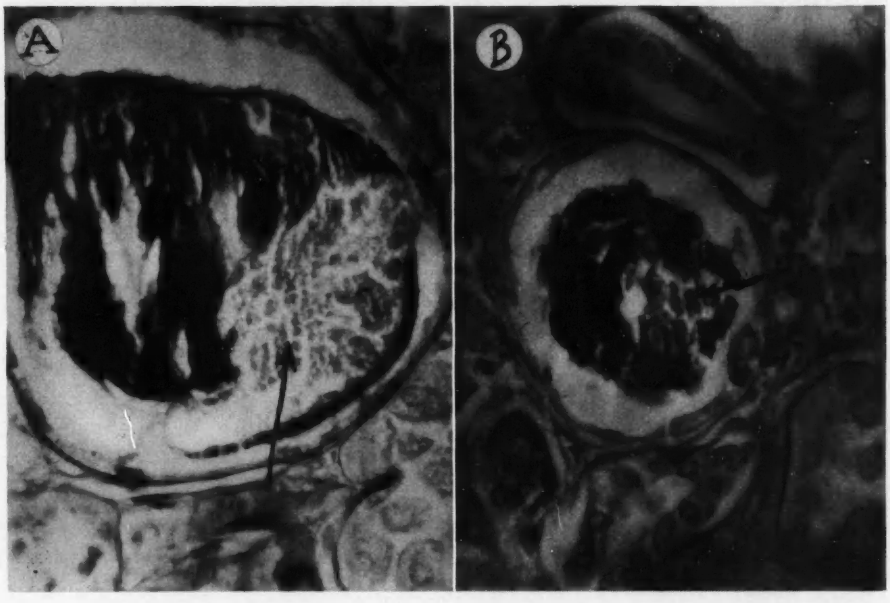

FIG. 4. PAS plus hematoxylin stain of human kidney with calculous disease shows within tubular lumen laminated cast PAS positive with hematoxylinophile material, probably of calcareous nature (oc.8× obj.45,Leitz).

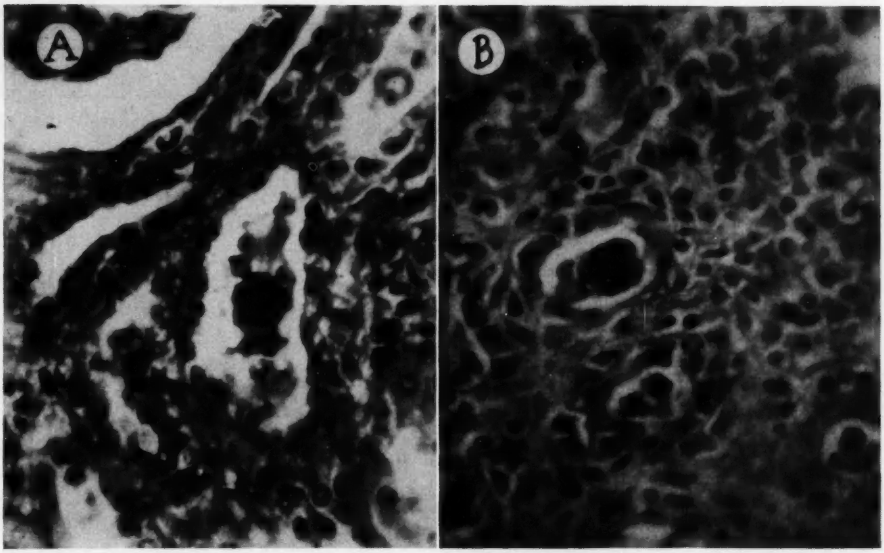

FIG. 5. Hematoxylin-eosin stain of human kidney with calculous disease shows within tubular lumen calcareous spheres surrounded by acidophilic material (oc.8× obj.45,Leitz).

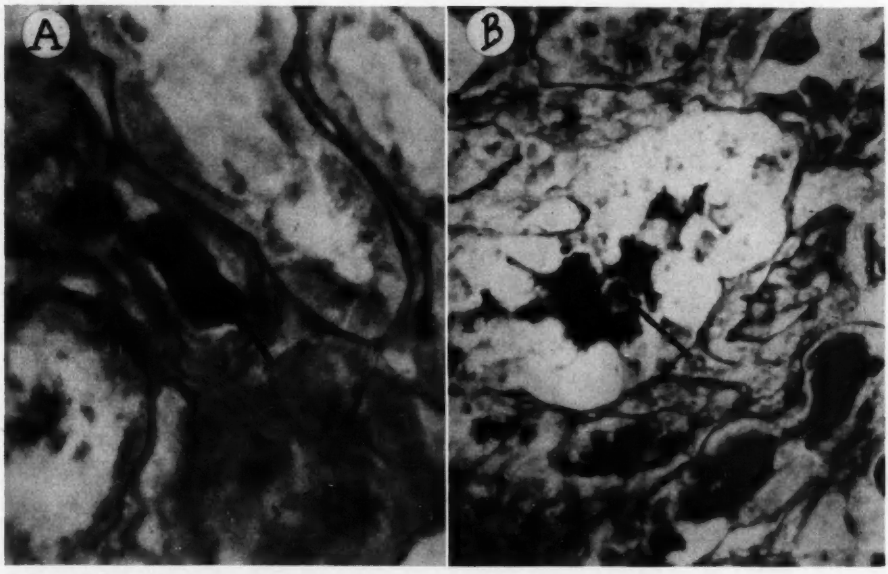

FIG. 6. PAS stain of human kidney with calculous disease shows (in negative appearance) calcareous spheres surrounded by PAS positive material within tubular lumen (oc.8× obj.45,Leitz).

In the human specimens examined by us no calcified granules were ever observed within the cytoplasm of tubular cells.

We found, however, several instances of markedly PAS positive casts with fine granular calcium deposits within the mucoprotein material.

Therefore, one has to admit the possibility of

calcium precipitability and binding to mucoproteins within the tubular lumen.

Although rather simple, this interpretation is more consistent with present knowledge of renal physiology and lends itself to speculation of which process actually determines calcium precipitability: enzymatic action of tubular cells[4] or some other factor which could constitute the common denominator in calculous disease.

SUMMARY

The authors call attention to the ever increasing interest in the role of mucopolysaccharides in nephrolithiasis and to the lack of observations of histochemical reactions in human specimens with calculous disease.

Using surgical specimens or renal biopsies in cases of nephrolithiasis the authors submit the renal tissue to different enzymatic reactions and stains which enable observation of calcium and mucopolysaccharides and an evaluation of the polymerization of the latter.

Increase of mucopolysaccharides was found in the basement membrane and brush border of the cells in the proximal tubule, as observed in experimental urolithiasis, but no calcification was ever found in these locations or within the cytoplasm of the cells as observed in different experiments.

The authors found in humans calcium containing casts of PAS positive material within the tubules and admit the possibility that precipitability and binding of mineral to mucoproteins may occur within the tubular lumen.

CALCULUS DISEASE IN A SINGLE KIDNEY

HOWARD I. SUBY

From the Department of Urology, Massachusetts General Hospital, Boston, Mass.

Management of patients with urinary calculi continues to be one of the most important urological problems and in certain cases there continues to be difference of opinion among urologists as to the advisability of surgery, the timing of surgery, and the operation of choice. This difference of opinion is the reason why certain patients are subjected to nephrolithotomy, whereas others with the same disease are subjected to nephrectomy. Therefore, before considering the problems of calculus disease in a single kidney, it seems wise to consider the original calculus problem which caused the patient to be left with one kidney. Absence of stone disease in one kidney with bad stone disease in the other is not uncommon. Figure 1, *a* is the roentgenogram of a 76-year-old woman who has had a large staghorn stone in her right kidney for 43 years but with a normal left kidney free of calculus disease during this long period of time. This patient must have had some unilateral renal abnormality but completely normal body metabolism. In her stone-free kidney she has normal renal architecture, normal renal metabolism, and she has an efficient ureterovesical valve. These are safety factors. She has had a "sick" kidney on her right side and a "healthy" kidney on her left side. Obviously no severe infection has involved her left kidney and there may be little or none of what causes the protein matrix of stones in urine from the left kidney.

Today more conservative kidney surgery is performed in an attempt to save good renal tissue. With the availability of blood banks long operations can now safely be done, and with the availability of chemotherapy and antibiotics operations are feasible now which would have been foolhardy only a few years ago. It would seem therefore that there should be fewer nephrectomies today. A careful consideration of the entire stone problem, however, must be made

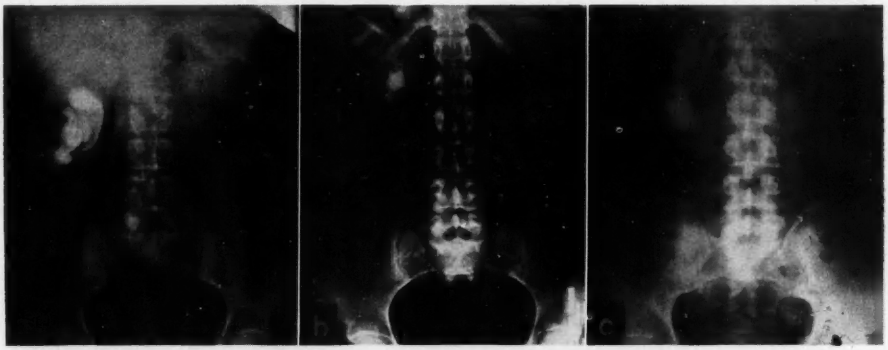

FIG. 1. *a*, Staghorn stone in right kidney 43 years in duration; normal left kidney. *b*, Single staghorn stone in right kidney. *c*, Multiple large and small stones in right kidney.

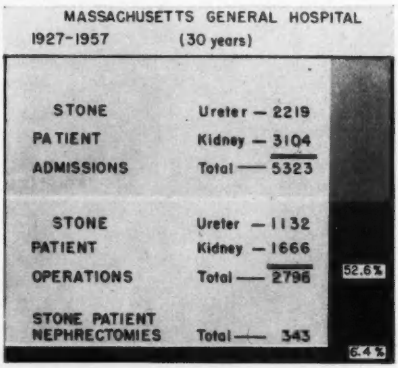

FIG. 2

before the operation of choice in any particular case can be determined. Figure 1, *b* is the roentgenogram of a 26-year-old woman who entered the hospital with a large staghorn stone of her right kidney. There was no stone in the left kidney region. An intravenous pyelogram showed good function of both kidneys and the ureters filled normally. The left kidney appeared entirely normal. A right nephrolithotomy was done and the stone was removed in one piece. This patient now has a completely normal-appearing urinary tract, and her urine, which originally contained Proteus bacillus, is now completely sterile.

Figure 1, *c* is the roentgenogram of a 42-year-old man who entered the hospital with multiple recurrent stones in his right kidney. No stones were visible in the left kidney. An intravenous pyelogram showed function in both kidneys but with a completely normal kidney on the left side and with a kidney full of stones, large and small, on the right. Since it seemed apparent that it would be impossible to remove all the stones from this diseased right kidney, nephrectomy seemed to be the operation of choice. Therefore, nephrectomy, though feared, may often be the treatment of choice.

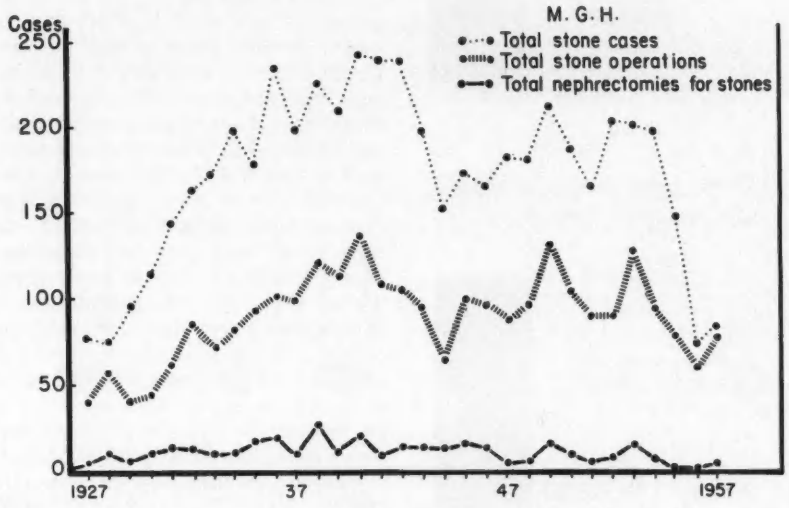

FIG. 3

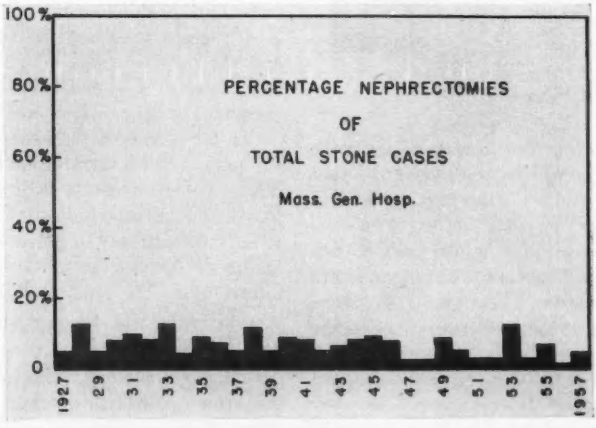

FIG. 4

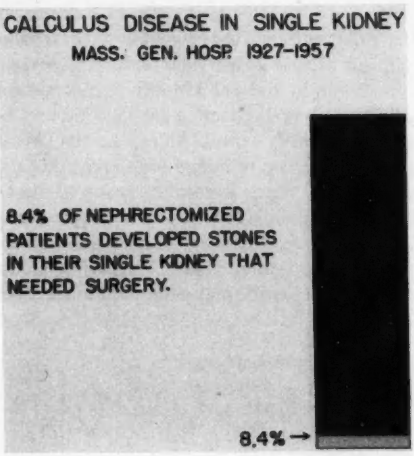
CALCULUS DISEASE IN SINGLE KIDNEY
MASS. GEN. HOSP. 1927–1957
8.4% OF NEPHRECTOMIZED PATIENTS DEVELOPED STONES IN THEIR SINGLE KIDNEY THAT NEEDED SURGERY.
8.4% →

FIG. 5

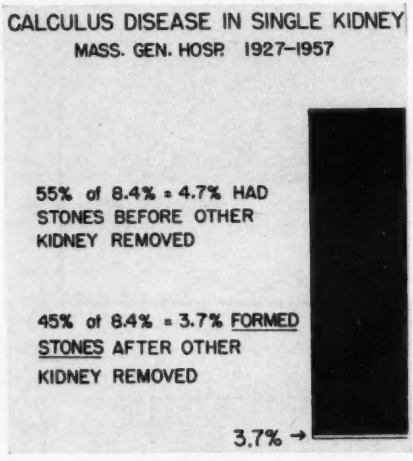
CALCULUS DISEASE IN SINGLE KIDNEY
MASS. GEN. HOSP. 1927–1957
55% of 8.4% = 4.7% HAD STONES BEFORE OTHER KIDNEY REMOVED
45% of 8.4% = 3.7% FORMED STONES AFTER OTHER KIDNEY REMOVED
3.7% →

FIG. 6

The surgical treatment of urinary calculi at the Massachusetts General Hospital during the past 30 years has been studied. The chart depicted in figure 2 is a summary chart of this 30 year follow-up study. There were 5323 "stone patient" admissions, 3104 with stones in the kidney and 2219 with stones in the ureter. There were 2798 "stone operations" in this period, 1666 operations on the kidney and 1132 operations on the ureter. Therefore, 52.6 per cent of the stone patients admitted were treated surgically. In this group there were 343 nephrectomies performed or 6.4 per cent of all of the patients with calculus disease who were admitted. Figure 3 is a summary chart; the top line shows the total number of stone cases admitted; the middle line, the total number of operations; the lower line, the total number of nephrectomies. The *percentage* incidence of nephrectomy by years was then determined. Figure 4 shows the percentage of the total stone patients by years who underwent nephrectomies. It is of some interest that this percentage is just about the same, plus or minus, in 1952 and 1955 as it was in 1945.

The subsequent course of nephrectomized stone patients was studied. We wanted to see what percentage and what type of stone problem caused trouble severe enough to necessitate further surgery. The number of these single kidneys that did cause trouble was small. Figure 5 shows that 8.4 per cent of nephrectomized stone patients acquired stones in their single kidney that necessitated further surgery. On closer analysis, however, it was found that 55 per cent of these nephrectomized patients who did have trouble had stones in their remaining single kidney before the other kidney was removed, whereas 45 per cent of the patients formed stones in their single kidney after their other kidney was removed. Therefore, multiplying the 55 per cent of the 8.4 per cent and multiplying 45 per cent of the 8.4 per cent we can observe that only 3.7 per cent of the nephrectomized patients really *formed* stones in their single kidneys (fig. 6).

What are the indications for surgery in these afflicted single kidneys? The first indication is anuria. Anuria in calculus disease is usually caused by a stone or cluster of crystals which blocks the urine somewhere between the kidney and the outside world. The most common site is the ureter. A second indication for surgery is persistent or very severe hematuria. A third indication for surgery is persistent pain which keeps the patient from carrying on his normal life or duties. Severe infection with a septic fever is a fourth and common indication for surgery. All of these conditions may be potential emergencies and anuria or oliguria necessitates prompt surgical intervention. The aims of surgery should be to establish adequate drainage of the urinary tract and if possible to restore the tract to normalcy. Figure 7 is a summary chart illustrating all the operative procedures on single kidneys for calculus disease performed at the Massachusetts

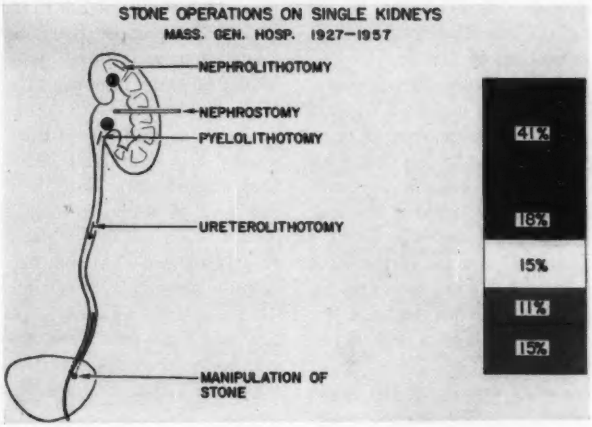

FIG. 7

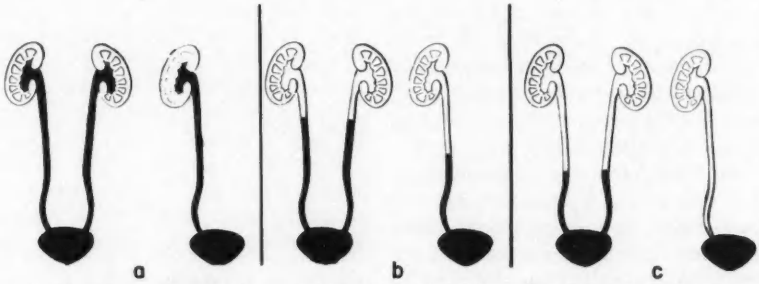

FIG. 8. Showing how rate of urine excretion in single kidney and ureter is twice that of normal (two kidneys and two ureters).

General Hospital. It is of interest that nephrolithotomy and nephrostomy, the two subdivisions on the top of the chart, comprise almost 60 per cent of all operations done on calculus disease in single kidneys, and that 15 per cent of all of these patients could be adequately managed by cystoscopic manipulation.

Why do nephrectomized stone patients do so well? They do well because the majority of these remaining single kidneys have normal renal architecture—normal ureteropelvic junctions and no difficulties in the infundibula. They do well because most patients with a single kidney have normal renal metabolism—normal urinalysis, normal acid-base regulating mechanism, normal total calcium present in the 24-hour urine, no abnormal urinary cystine and normal blood calcium, phosphorus and uric acid. In addition to this most of these patients have a normal efficient ureterovesical valve, one which enters

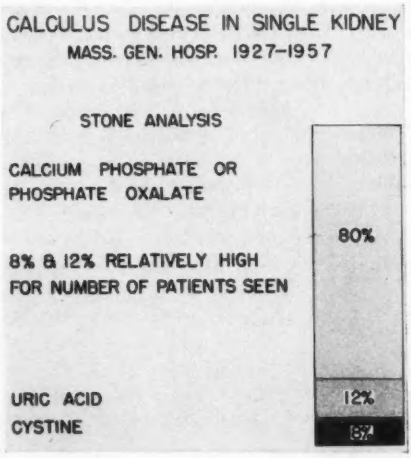

FIG. 9

obliquely and prevents infected urine in the bladder from going up into the good kidney. These are all important safety factors.

What important change occurs after nephrectomy? On a standardized food and fluid regimen the patient excretes the same amount of urine per hour after nephrectomy as he did before his operation. It is obvious that there is the same amount of excretion from the bladder per hour whether the patient has two kidneys or whether he has only one kidney. This urine furthermore contains the same amount of total salts and excreta as before nephrectomy. After nephrectomy one mechanical change, important in stone-forming patients, has occurred. The *rate* of urine passage out of the kidney and down the single ureter has been doubled after nephrectomy. Figure 8 shows that the "current" of water running down the ureter from the single kidney goes twice as fast as the "current" of water in the ureters of patients with two kidneys. There are two full excursions of a fixed amount of urine down the single ureter to one full excursion of the same amount of total urine down the two ureters, on the same fluid intake. Fluids therefore are automatically being forced, and small stones or cluster of crystals are apt to be washed out.

"Calculus disease" in a single kidney differs from "a stone in a single kidney or ureter." I am now referring to the underlying disease that caused the stone and not to the actual stone emergency. The preoperative "metabolic picture" of nephrectomized stone patients whose other kidney or ureter later needed surgery was studied. We were interested to learn what disease these patients had that caused them to be left with one kidney and then later necessitated surgery on their single kidney. Stone analysis, of course, was one way of studying their underlying calculus disease. Figure 9 shows that 80 per cent of these reoperated stone patients had stones made up of calcium phosphate or calcium-phosphate-oxalate complex. It shows that 12 per cent were of uric acid and 8 per cent were of cystine. This 12 per cent and 8 per cent is a relatively larger percentage than the actual number of cases operated on because there were fewer nephrectomies for calculus disease of these types. The underlying calculus disease, whether it be an upset in the metabolism of uric acid, cystine, calcium, phosphate, or oxalate should be studied and treated diligently and constantly. Freedom from surgical disease in single kidneys may often be insured by adequate medical treatment if the patient has the safety factors—normal renal architecture, normal renal metabolism, and normal ureterovesical valve, plus Nature's new safety factor caused by nephrectomy—the increase in rate of urine coming out of the single kidney and ureter.

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DISCUSSION

Dr. William H. Boyce (Winston-Salem, N. C.): I would like to congratulate my fellow members of this program for the fundamental research they have reported this morning.

Dr. McDonald's work is most interesting. We have done some studies in regard to the influence of hormones on the concentration and composition of total nondialyzable solids (TNDS) of normal urine. Patients with hyperthyroidism often have hypercalcinuria (300 to 500 mg./24 hrs.), but we have never found one of these patients to have formed a urinary calculus. Gross thyroid hormone has been separated into several fractions which differ in their principal physiologic effects. Several preparations were made available through the courtesy of the Armour Company. Gross thyroid extract (Thyrar) was administered in dosage of 5 to 8 gr. daily to six young adult volunteers. We found no significant variation in the amount (dry weight) of total nondialyzable material in the urine after as long as 30 days of medication. There was a significant reduction in the "sialic acid" content of the TNDS from a normal mean value of 9.7 per cent of the total to near zero in every subject. There appears to be a relative reduction in "sialic acid" content of TNDS from patients with renal calculi. Stone matrix differs from uromucoid by the absence of sialic acid from the former. The interpretation of this observation will require much additional data. None of these patients developed hypercalcinuria and cannot be considered as hyperthyroid subjects.

In spite of the difficulties in reproducing endocrinopathies experimentally there is certainly a broad vista opening in this area where Dr. McDonald has begun his investigations.

In regard to Dr. DeAlbuquerque's paper, we have done similar studies on autopsy, biopsy and surgical specimens from the kidneys and collecting portions of the urinary tract. Our results were identically the same and I think our conclusions were in complete accord with his.

Histochemistry, in its present stage of development, is an exceedingly nonspecific method for detecting molecular changes in tissues. The basic changes in mucoid structure of patients with calculous disease appear to be in a more subtle molecular change than the present histochemical techniques will permit us to detect.

This applies to the metachromasia producing dyes as well as the periodate Schiff leucofuchsin reaction. We have found that both lyophilization and removal of phosphate from metachromatic stone matrix will reduce or destroy the metachromasia.

Dr. Donald F. McDonald (Seattle, Washington): If our studies call attention to only one thing they will be very well worth while, and that is that stones can dissolve. Many of us have never been convinced that this can happen. Our animal experiments have convinced us.

President Cahill: Perhaps we are having another revolution in urology. We saw the disappearance of venereal disease, and perhaps the stone will go, too. What do you think about that, Dr. DeAlbuquerque?

Dr. Paulo F. DeAlbuquerque (Rio de Janeiro, Brazil): There is nothing actually to be added to what has been said, but I must agree with Dr. Boyce that with all the accumulation of literature on mucopolysaccharides in stone formation, which we have all followed in the last few years, I think information is still very tenuous and that we probably are dealing with peripheral factors rather than with basic data.

However, if anyone is interested in stones, I think one has seldom hit a more promising field. Although the techniques are still dubious, I think it is a field that should really be pursued, because probably the common denominator of stone formation lies with mucopolysaccharides.

ENZYMES

WILLIAM P. HERBST, JR.

From Department of Urology, Georgetown University School of Medicine, Washington, D. C.

The demands on the time of physicians in discharging their responsibilities in their practice preclude delving in basic science to any appreciable degree.

My reason for presenting these data was having had the opportunity of reading a thesis by Peggy Ann Stubbs entitled, "The Effect of Enzymes on Chromosomes."

The potentialities of this field make it theoretically possible to predict the course of homeostatic patterns from the time of conception to death.

The following paragraphs are the premises of emzymology from Potter's ENZYMES, GROWTH AND CANCER.

"1) Each biochemical reaction is catalyzed by an enzyme. These compounds exert a directing influence by making the reaction proceed so rapidly in one direction that side reactions are nullified.

"2) Enzymes are chemical compounds.

"The generalization 'no enzyme without protein' appears established as one of the most widely based inductive rules in the field of chemistry, and, indeed, it is often speculated that all proteins might be enzymes of one sort or another. Because of the relation of such compounds to amino acids, the alternative paths of combustion and systhesis are apparent. A balance exists between the two processes according to the amount of catabolic and anabolic enzymes.

"3) The function of a tissue is the resultant of the organization of its enzymatic components.

"When an enzyme reacts with its substrate and thus catalyzes a chemical transformation, two separate but dependent processes are involved: There is combination to form the enzyme-substrate complex and decomposition to yield enzyme and transformed substrate. The regenerated enzyme may again pass through the cycle. This ability is probably based not only upon the "fit" between enzyme and substrate but also on the ability of the enzyme to react with other molecules that restore it to its original form. It is the latter that makes it possible for one enzyme molecule to activate many substrate molecules successively.

"4) Enzyme activity is not always equal to enzyme concentration. The reaction may be slightly or markedly altered by changes in the substrate concentration, inhibitors, temperature, and the hydrogen ion concentration.

"5) Specific enzymes can be specifically inhibited.

"Such a phenomenon is accounted for by the fact that enzymes differ from other catalysts in possessing marked specificity of action: they show absolute specificity, stereochemical specificity, and relative specificity. So far as can be determined there is no explanation for such action. Rather, a given agent may owe its ability to affect one organism and to leave others unharmed to a metabolic difference in the two, whereas a second agent may depend on physical factors. Or the selectivity may be the resultant of several aspects with one predominating."

The digestive enzymes such as pepsin and pancreatin were used many years ago as therapeutic agents in indigestion. Today we are finding clinical use for such enzymes as streptokinase, streptodornase and trypsin in attempting to modify the basic mechanism of inflammation in any and all acute inflammatory entities.

We are using enzyme inhibitors in renal metabolic processes in most spectacular ways. Diamox and diuril, carbonic anhydrase inhibitors, presented fully in brochures from the pharmaceutical houses that make and sell them, are examples.

We rely upon studies in enzyme kinetics to diagnose prostatic malignancies. We use enzyme analysis to direct therapy in prostatic malignancies.

We use many different therapeutic agents which have as their target enzymes that form and dissolve blood clots and modify tissue capillary permeability. The subject of coagulation is most complex and is very incompletely understood at this time.

In the field of endocrinology the pharmaceutical houses rely upon enzymes to make many

steroids and enzymes really elaborate all of our endocrines which maintain our homeostatic patterns. The relationship of the steroids to enzymes is currently most important in that the clinical use of antiphlogistic steroids in shock, general resistance, acute inflammatory lesions, etc., is a most important aspect of current modern therapy.

Perforation of intestinal tract ulcers is explained as follows:

The cells which make up the wall of intestinal tract ulcers are damaged or substandard functioning cells in which various enzyme activity is appreciably depressed. The difference between a damaged and necrotic cell in some instances is very slight so that all that is needed to kill a cell is a little more enzyme inhibition. All of the antiphlogistic steroids and ACTH are potent enzyme inhibitors and it is their inhibitory action which so spectacularly influences an inflammatory process.

In the field of prognosis of malignancy we are at the end of our statistical pathological potentialities. Malignancy is involved chiefly with enzyme mechanisms. Projects utilizing cytochemical stain techniques, as described by Kelly, may improve our ability to prognosticate the expectancy of patients with prostatic cancer.

Any project which results in identifying a specific enzyme stimulator or inhibitor is a link in the chain of comprehending what malignancy is.

In the field of oxalate urinary tract calculus formation, any enzyme which could be identified as producing a large amount of oxalate in hepatic cells might well prove valuable in future control of oxalate calculus formation.

In the field of fertility, enzyme action is a very active aspect of research now going on.

The potentialities of tagged enzyme research are limitless.

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CYSTITIS GLANDULARIS

W. E. KITTREDGE AND WILLIAM BRANNAN

From the Department of Urology, Ochsner Clinic, New Orleans, La.

Cystitis glandularis has aroused the interest of many authors since it was first described by Stoerck[1] in 1899. The recent diagnosis of this interesting lesion in a boy 4 years old prompted a review of six of these cases diagnosed by microscopic examination of tissue obtained at biopsy at Ochsner Foundation Hospital, together with one case known to the junior author at the Johns Hopkins Hospital. It was hoped that review of these 7 cases might throw some light on the etiology and significance of this lesion. We purposely excluded cases of exstrophy of the bladder, since this represents a particular congenital anomaly in itself and lends some confusion to the subject as a whole.

Cystitis glandularis represents a proliferative lesion of the vesical mucosa showing gross evidence of change in the normal surface architecture in which the lining epithelium takes on an irregular, mammalated appearance. This may be striking and the cause of some alarm, since it is not unlike the appearance of some neoplasms of the bladder. Microscopically, the mucosa is thrown into folds and the submucosal region is occupied by glandular elements, usually accompanied by chronic inflammatory changes. Emmett and McDonald[2] divided these glands into two types. One is the "intestinal type," in which the lining epithelium of the glands is columnar, consisting of a single cell layer with basal nuclei with the cells themselves filled with mucus, giving the impression of goblet cells of the intestine. This is also the variety of glands characteristic of cystitis glandularis as described by Hinman and Cordonnier.[3] The second, or "subtrigonal type," consists of glandular spaces or cysts lined with multiple layered squamous or transitional cells, only the surface epithelium being of the columnar variety. This type is usually found near the vesical neck and bears close resemblance to those glands described by Albarran.

The history and etiology of cystic changes in the vesical epithelium were thoroughly reviewed by Morse[4] in 1928. He described the interesting work of von Brunn, who described epithelial cell nests originating from epithelial buds as a result of chronic inflammation, and reviewed the cystic changes that bear the name cystitis cystica. He completely summarized the information up to that time concerning the possibilities of change in the cell nests into cystic structures, as believed by Stoerck[1] and others. Morse[4] offered the following theories of the cause of cystic change in the bladder: 1) inflammatory closure of glands in the urinary tract, 2) inflammatory closure of crypts of the mucous membrane, 3) paracytic invasion of the urinary bladder, and 4) degeneration or secretory changes in the cell nest of von Brunn. He himself failed to demonstrate gland formation or glandular elements in relation to the cysts of cystitis cystica except in the region of the trigone, close to the vesical neck.

More recently, Stirling and Ash,[5] from a review of 7 cases of cystitis glandularis, concluded that cystitis cystica and cystitis glandularis probably represent different stages of the same process, all related to chronic inflammation. They thought that the cell nests of von Brunn are merely incomplete "blind end" sections of invaginated epithelium. They thoroughly discussed the presence of normally occurring glandular elements in the urinary bladder and there appears to be no definite proof that glandular elements are present in the bladder of the newborn infant.

Most authors agree that chronic irritation of the lining epithelium of the urinary bladder, from infection or even from obstructive disease, must be present for the change to occur. Emmett and McDonald[2] found evidence of chronic inflamma-

[1] Stoerck, Okar: Beiträge zur Pathologie der Schleimhaut der harnleitenden Wege. Beitr. z. path. Anat. u. z. allg. Pathol., **26:** 367, 1899.

[2] Emmett, J. L. and McDonald, J. R.: Proliferation of glands of the urinary bladder simulating malignant neoplasm. J. Urol., **48:** 257–265, 1942.

[3] Hinman, F. and Cordonnier, J.: Cystitis follicularis. J. Urol., **34:** 302–312, 1935.

[4] Morse, H. D.: The etiology and pathology of pyelitis cystica, ureteritis cystica and cystitis cystica. Am. J. Path., **4:** 33–50, 1928.

[5] Stirling, W. C. and Ash, J. E.: Chronic proliferative lesions of the urinary tract. J. Urol., **45:** 342–360, 1941.

tion in most of their 9 cases. In 1944 Foot[6] concluded, from a review of 4 cases of glandular metaplasia of the urinary tract, that the process originates in the most superficial cells of the lining epithelium. He believed that the process is definitely metaplastic except when it occurs near the fundus of the bladder, when it could arise from urachal remnants. However, Patch[7] did not agree that all glandular elements in the fundus are urachal remnants because the urachal epithelium is similar to that of the bladder. He concluded that both leukoplakia and glandular change are the result of epithelial metaplasia in response to a call for altered function or at least as a result of altered environment. The extent and intensity of the metaplastic process are in direct relation to the intensity and duration of the inciting factor. In an earlier review of cases of cystitis cystica and cystitis glandularis, Patch and Rhea[8] concluded that a series of consecutive changes takes place beginning with the cell nest of Brunn, proceeding first to cystitis cystica by a secretory change and finally to cystitis glandularis with its columnar, mucus-secreting cells. The cells may spread over the surface epithelium from the gland.

In discussing the two types of columnar cells found in glandular change, Pund and associates[9] believed that the embryologic development of the bladder plays a large role. He proposed that the intestinal or goblet cell type gland occurs more frequently in the dome of the bladder since this is embryologically entodermal in origin and metaplasia will direct itself to this end. Similarly, the trigone is of mesodermal origin and metaplasia will be in the direction of epithelium more closely resembling prostatic epithelium. In addition, ectopic nests of glandular epithelium occurring in the dome will be of entodermal type, and hormonal changes may direct the trigonal epithelium to resemble prostatic tissue. In discussing a case of cystitis glandularis coexisting with cystitis follicularis, Kretschmer[10] also mentioned these possibilities. This theory may be an adequate explanation for the majority of cases but Sauer and Blick[11] reviewed 7 cases of cystitis glandularis in 1948 and described the two pathologic types but could find no correlation between the location and the cell type.

In a comprehensive review of the pathogenesis of cancer in the bilharzial bladder, Makar[12] frequently found changes in the vesical epithelium which he described as "cystitis pseudoglandularis." These consisted of glandular elements lined with a columnar epithelium involving the submucosa in association with bilharziasis with its severe chronic inflammatory reaction. He also noted occurrence of these glandular elements in association with "columnar cell carcinoma" of the bladder, although the squamous and epidermoid types of carcinoma predominated. Of great interest is the fact that these benign glandular changes were apparently reversible in certain cases by diversion of the urine away from the bladder.

Since cystitis glandularis is usually associated with chronic inflammation, there are no pathognomonic symptoms that can be related to the entity itself. In Sauer and Blick's[7] patients, frequency and dysuria predominated (5 patients), and painful hematuria was present in 3 patients. All but one of Emmett and McDonald's patients complained of dysuria. The symptoms in a case reported by Baker[13] in 1947 were apparently secondary to chronic infection and a ureterocele complicated by calculous formation. Lowry, Hamm, and Beard[14] reported 3 cases of extensive glandular metaplasia in the region of the vesical neck and trigone which caused primarily obstruc-

[6] Foot, N. C.: Glandular metaplasia of the epithelium of the urinary tract. South Med. J., **37:** 137–142, 1944.

[7] Patch, F. S.: Epithelial metaplasia of the urinary tract. J.A.M.A., **136:** 824–827, 1948.

[8] Patch, F. S. and Rhea, L. J.: The genesis and development of Brunn's nests and their relation to cystitis cystica, cystitis glandularis and primary adeno-carcinoma of the bladder. Canad. Med. Assn. J., **33:** 597–606, 1935.

[9] Pund, E. R., Yount, H. A. and Blumberg, J. M.: Variations in morphology of urinary bladder epithelium; special reference to cystitis glandularis and carcinomas. J. Urol., **68:** 242–251, 1952.

[10] Kretschmer, H. L.: Cystitis glandularis and follicularis. Am. J. Surg., **82:** 198–201, 1951.

[11] Sauer, H. R. and Blick, M. S.: Cystitis glandularis; a consideration of symptoms and clinical course of the disease. J. Urol., **60:** 446–458, 1948.

[12] Maker, N.: A note on the pathogenesis of cancer in the bilharzial bladder. Brit. J. Surg., **45:** 240–250, 1957.

[13] Baker, W. J.: Cystitis glandularis associated with ureteral stone and ureterocele. Quart. Bull. Northwestern Univ. M. School, **21:** 242–244, 1947.

[14] Lowry, E. C., Hamm, F. C. and Beard, D. E.: Extensive glandular proliferation of the urinary bladder resembling malignant neoplasm. J. Urol., **52:** 133–138, 1944.

tive symptoms, infection being found in only one case. In those cases discovered incidentally at operation for relief of prostatic obstruction, it is difficult to associate any of the symptoms with glandular metaplasia.

Although most observers consider cystitis glandularis simply cellular metaplasia secondary to chronic irritation, others believe that it may be the precursor of adenocarcinoma of the bladder. Patch and Rhea[8] and Emmett and McDonald[2] believed that cystitis cystica, and more especially cystitis glandularis, are potentially precancerous lesions, the precursor of mucus-secreting adenocarcinoma. Immergut and Cottler[15] and Foot[6] reported single cases of adenocarcinoma associated with cystitis glandularis. However, adenocarcinoma is frequently found without evidence of benign glandular metaplasia, as in the 3 cases reported by Patch and Pritchard.[16] Sauer and Blick[11] considered cystitis glandularis to be a chronic disease, which may remain stationary for an indefinite period of time, and recommended conservative treatment. All authors emphasize that it may be difficult to distinguish between cystic, follicular, or glandular changes and carcinoma without adequate biopsy. Actually, most cases of glandular metaplasia will first be called carcinoma on cystoscopic examination and later will be proved to be benign metaplasia by histologic examination. The importance of adequate biopsy in any questionable case has been recently emphasized by Nesbit,[17] who reported an interesting case of carcinoma of the bladder arising in cystitis cystica and treated by total cystectomy. He recommended multiple biopsies in all cases in which cystic change is seen

REPORT OF CASES

Case 1. A white man, 37 years old, was seen in January 1949. In 1939 and again in 1946 he had been treated by massage for prostatitis. He had no other urinary symptoms and specifically neither hematuria nor pyuria.

On general physical examination no abnormalities were detected except for a moderate amount of pus in the prostatic fluid. Results of urinalysis were normal. The blood urea nitrogen value was 16 mg. per cent. No abnormalities were detected in intravenous urograms.

The prostatitis improved with treatment and the patient was not seen again until April 1952, when he returned with total, gross, painless hematuria. Cystoscopy disclosed an angry, elevated, irregular area occupying the left half of the trigone below the left orifice but extending to the vesical neck on the left. The prostate was again infected but otherwise unchanged. The urine was uninfected.

Transurethral biopsy was performed and the area fulgurated. Postoperatively, the patient did well but at cystoscopy three months later the process was seen to have extended over the remainder of the trigone. The entire area was again resected and thoroughly fulgurated. Subsequent examinations at intervals of from six to nine months have continued to show several small isolated cystic areas in the trigonal region gradually increasing in size. The patient has remained asymptomatic, the prostatitis has subsided and in recent intravenous urograms the only abnormality was a small stone in the right kidney.

On histologic examination (fig. 1) there was evidence of extreme thickening of the submucosal layers of the bladder with edema and connective tissue proliferation. Throughout this submucosal tissue were scattered nests of cells typical of the cell nests described by von Brunn, some of which had progressed to cyst formation. In certain areas the mucosal lining of the cysts had taken on a columnar appearance but no active secretion was evident. There was also evidence of considerable round cell infiltration.

Case 2. A white man, 32 years old, had noted pain in the right groin 18 months before admission. After cystoscopy and retrograde pyelography he was told that there was obstruction of the right ureter and that he had a cyst in the top of his bladder. Thereafter right epididymitis developed but gradually subsided only to recur again one year later. The only urinary symptoms were slight increase in frequency and mild burning. He had no pyuria.

Results of general physical examination were normal. The prostate was infected and the seminal vesicle on the right was indurated and tender.

Results of urinalysis were normal. Slight dilatation of the lower thirds of both ureters was

[15] Immergut, S. and Cottler, Z. R.: Mucin-producing adenocarcinoma of the bladder associated with cystitis follicularis and glandularis. Urol. & Cutan. Rev., **54:** 531–534, 1950.

[16] Patch, F. S. and Pritchard, J. E.: Mucinous adenocarcinoma of the bladder. J. Urol., **57:** 126–132, 1947.

[17] Nesbit, R. M.: Is cystitis cystica an innocent or a malefic lesion? J. Urol., **75:** 443–447, 1956.

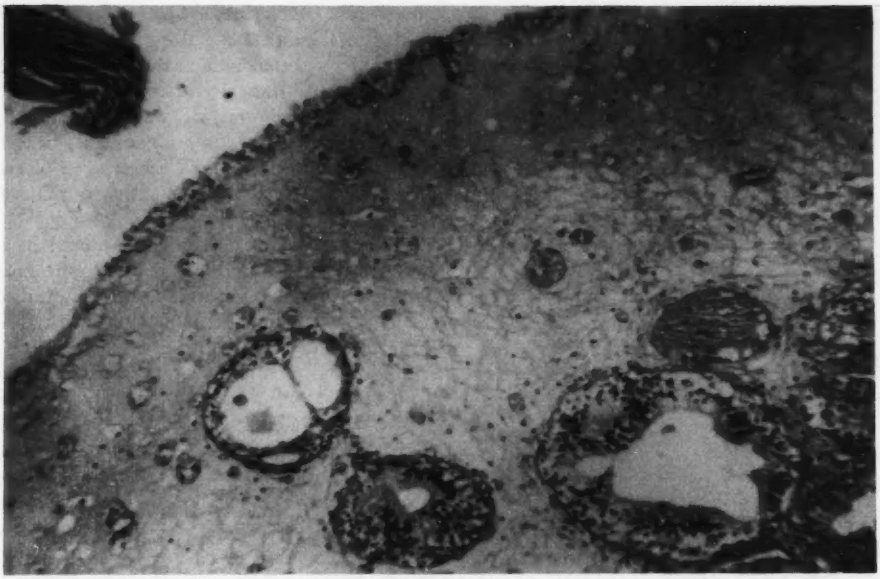

FIG. 1. Case 1. Photomicrograph showing cuboidal change in surface epithelium plus submucosal edema. Several cysts, two of which are lined with columnar epithelium, are seen.

noted in the intravenous urograms. The blood urea nitrogen value was 16 mg. per cent.

Cystoscopy disclosed the trigone, vesical neck and proximal prostatic urethra to be covered with a cystic process, some of the cysts being large and pedunculated. This process obscured the ureteral orifices but the remainder of the bladder appeared to be normal.

Transurethral resection was done, and postoperatively, two bouts of bleeding required catheter drainage and transfusion, but thereafter the patient did well. Efforts to contact the patient since discharge from the hospital have been unsuccessful.

On histologic examination (fig. 2) the surface epithelium in areas was somewhat thickened and dipped into the submucosal regions in the form of crypts and buds. In other areas the most superficial layers of epithelium had undergone a columnar change. The submucosa was greatly thickened and rather vascular with infiltration of leukocytes. Throughout the submucosa there were numerous cysts of varying size, some close to one another with only a basement membrane between them. The cells lining the cysts were of varying thicknesses but in general the most superficial layer was of a columnar type with basal nuclei. The pathologic diagnosis was cystitis cystica and cystitis glandularis.

Case 3. A white boy, 4 years old, had an attack of periumbilical pain, urinary frequency and urgency, associated with fever, five months before admission. An intravenous urogram was reported to demonstrate no abnormalities and a diagnosis of functional frequency was made elsewhere. Frequency developed to the point of incontinence. Another urologist was consulted who, on cystoscopy, made a diagnosis of interstitial cystitis associated with bilateral vesical ureteral reflux. The urine culture showed Pseudomonas aeruginosa. Treatment consisted of administration of terramycin, furadantin, banthine, and instillations of a 2 per cent solution of silver nitrate.

When seen at the Ochsner Clinic, the child still had urinary frequency to the point of incontinence and the urine was grossly bloody. On physical examination the blood pressure was 100 mm. Hg. systolic and 65 mm. Hg. diastolic and the rectal temperature was 100.4F. The child appeared healthy and on general physical examination no other abnormalities were noted.

Urinalysis disclosed grossly bloody urine. Urine culture grew a Pseudomonas organism. Intrave-

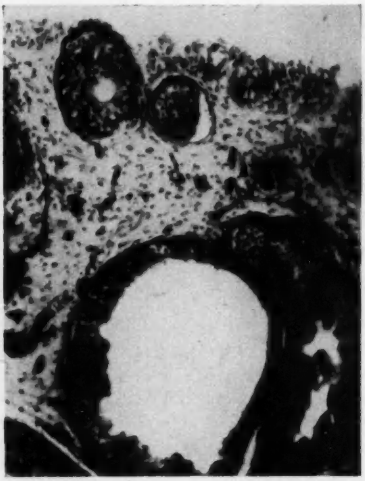

FIG. 2. Case 2. Representative area showing tall columnar epithelium lining cyst lumen.

nous urograms disclosed normal upper urinary tracts and a cystogram revealed a normally shaped bladder with right vesicoureteral reflux.

Cystoscopy after induction of general anesthesia disclosed a normal bladder, trigone and vesical neck except for several hemorrhagic areas and a number of raised mucosal lesions occupying 3 to 4 cm. near the dome of the bladder on the right posterior lateral wall. The bladder was then explored through a suprapubic approach, and biopsy and thorough fulguration of this area were accomplished.

Postoperative recovery was uneventful and gradual improvement in symptoms was noted. The infection subsided completely with use of mandelamine. Cystoscopy two months later disclosed only two tiny areas of hyperemia near the dome and these were fulgurated.

On histologic examination (fig. 3) of sections of the bladder, areas of calcification were seen, and just deep to the ulcerated mucosa were irregular, somewhat glandular spaces lined by fairly large cells having clear cytoplasm. The capillaries were greatly dilated, and a variety of inflammatory cells was seen.

The pathologic diagnosis was chronic cystitis with calcification and areas of cystitis glandularis.

Case 4. A white man, 55 years old, was admitted to Ochsner Foundation Hospital because of complete urinary retention. He had had gradually progressive prostatism for the preceding five years. He had never had pyuria but he had noted total painless hematuria on two occasions.

On physical examination the only abnormality was slight prostatic hypertrophy considered to be benign. The prostate was not infected.

On urinalysis the only abnormality was the presence of blood, due to the trauma of catheterization. The blood urea nitrogen value was 14 mg. per cent.

At cystoscopy an obstructing median lobe and some intrusion of the lateral lobes were noted. There was nothing abnormal other than trabeculation in the bladder. The prostate was resected transurethrally.

The postoperative course was complicated by osteitis pubis, which eventually responded well to deep roentgenotherapy.

Histologic examination (fig. 4) of the tissue showed it to consist of recognizable prostatic elements with pronounced fibrous hyperplasia. In other areas, presumably from the trigonal region of the bladder, the mucosa was thickened, sending buds and crypts down into the submucosa. In some areas there was unmistakable cystitis cystica with varying sized cystic spaces, many of which were lined by columnar epithelium with basal nuclei. In other areas there was a tendency toward squamous metaplasia of the surface epithelium but there was little evidence of chronic inflammation as might be represented by pronounced round cell infiltration and edema. The pathologic diagnosis was fibrous hyperplasia of the prostate, cystitis cystica and cystitis glandularis.

Case 5. A white man, 61 years old, was seen because of gradually progressive burning, frequency, and urgency of urination associated with cramping low abdominal pain and passage of gas and fecal matter in the urine, of three years' duration. He had been told by several physicians that his urine was infected. He had had complaints referable to the gastrointestinal tract compatible with a mild inflammatory or obstructive process.

On general physical examination the only abnormal finding was slight hypertension and obesity. The prostate, although infected on smear, was not impressive and felt benign.

Urinalysis showed a trace of albumin, many white blood cells, and bacilli. The blood urea nitrogen value was 17 mg. per cent. Results of intravenous urography were essentially normal

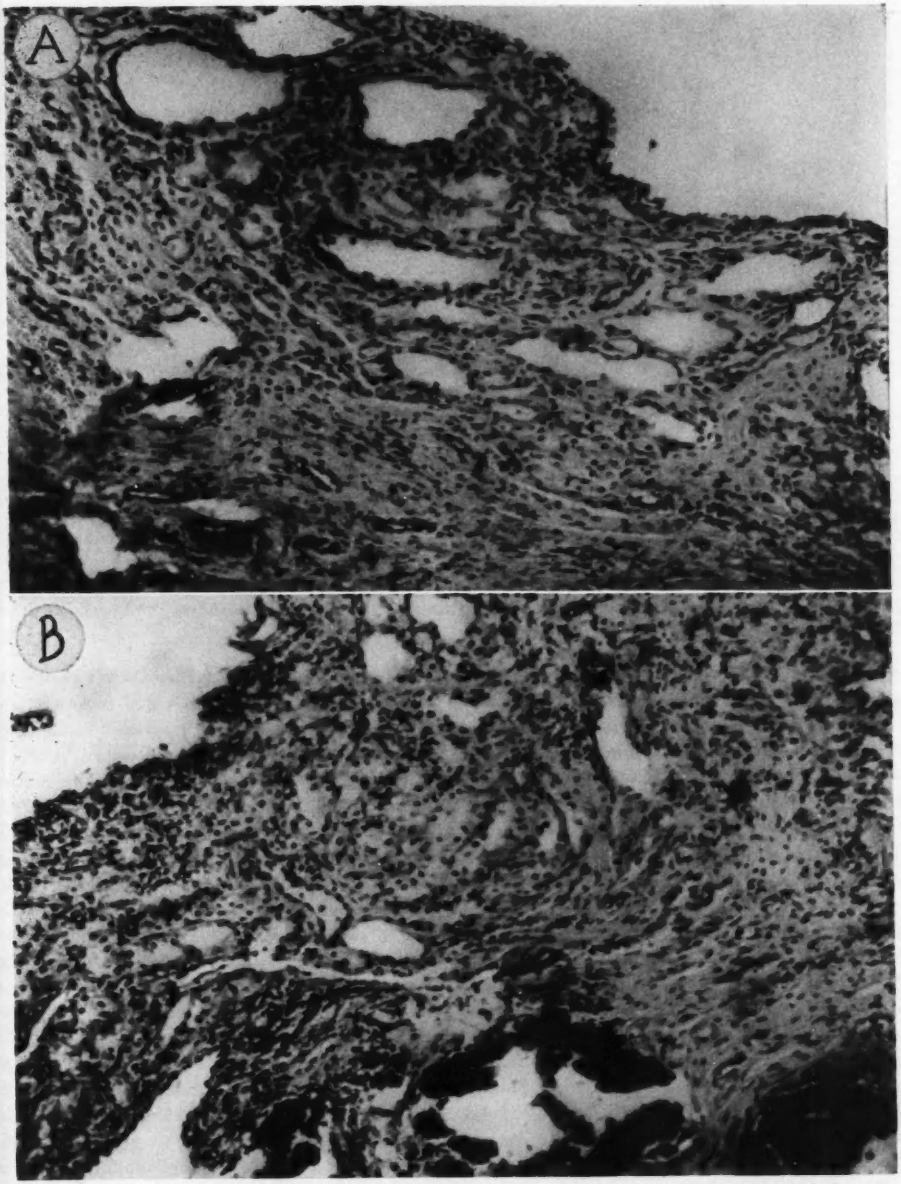

FIG. 3. Case 3. *A* and *B* both show diffuse glandular change beneath ulcerated epithelial surface. Calcification is seen in *B*, and several cystic spaces appear in *A*.

and a cystogram failed to show any communication with the gastrointestinal tract. Roentgenologic examination with barium enema disclosed a constricting lesion in the sigmoid.

Cystoscopy showed a small fistulous opening in the midline of the bladder behind the trigone. Surrounding this were chronic inflammation and granulation tissue, and generalized bullous

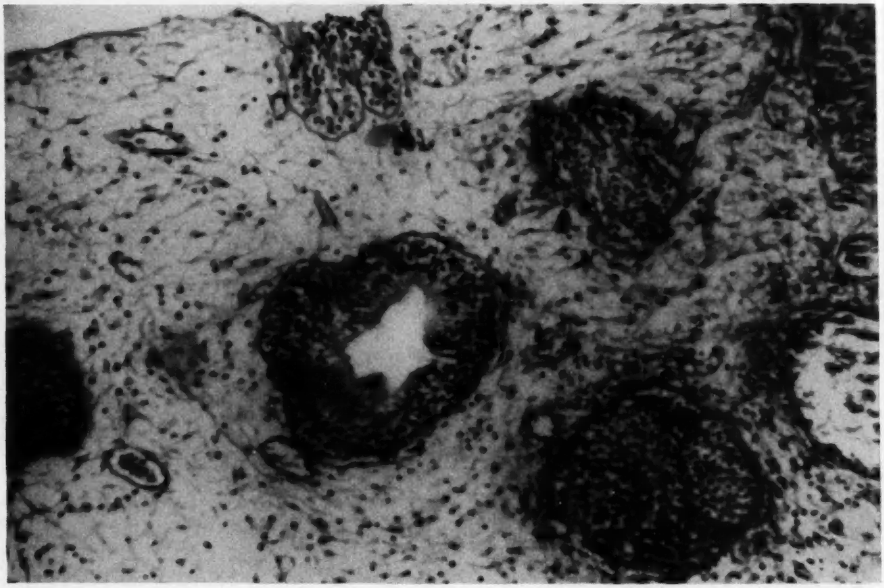

FIG. 4. Case 4. Epithelial bud is present on surface, and in submucosa there are "cell nests" and one cyst lined with columnar epithelium.

edema and injection of the bladder mucosa were noted.

Transurethral biopsy of the tissue surrounding the fistulous opening was performed followed by resection of the sigmoid and closure of the bladder. The postoperative course was uneventful.

On histologic examination (fig. 5) the lining epithelium of the bladder, where seen, was of a columnar type and, in areas, sent gland-like processes into the submucosa. In the submucosa there was pronounced evidence of chronic inflammation with round cell infiltration and follicle formation. Scattered around in the submucosal areas were many gland-like structures lined with a single layer of columnar epithelium with basal nuclei. Many columnar cells were vacuolated and appeared definitely of a secretory variety. The pathologic diagnosis was vesicocolic fistula associated with severe chronic cystitis and cystitis glandularis.

Case 6. A white woman, 37 years old, was admitted to Ochsner Foundation Hospital on April 3, 1947, complaining of inability to void and to have normal bowel movements, since having a caudal anesthetic during delivery of a normal child six months before admission. Paralysis of the right leg and paresthesia of the skin in the lower extremities and perineum also developed. The paralysis gradually disappeared but the patient had never regained the ability to empty her bladder and urine escaped when the bladder became distended. She had been catheterized about every six hours since the delivery and had been known to carry several ounces of infected residual urine. She denied any previous urinary symptoms.

The patient appeared healthy and results of general physical examination were normal except for the bladder, which could be percussed one or two fingerbreadths above the symphysis pubis. Also hypesthesia was noted over the perineal region.

Urinalysis disclosed grossly infected urine containing many white blood cells, cocci, and bacilli. The intravenous urogram disclosed normal upper urinary tracts, and evidence of trabeculation and early cellular formation was seen in the retrograde cystogram. There was no vesicoureteral reflux.

Cystoscopy disclosed a moderately trabeculated bladder with evidence of chronic infection, particularly around the trigone. Some obstructing

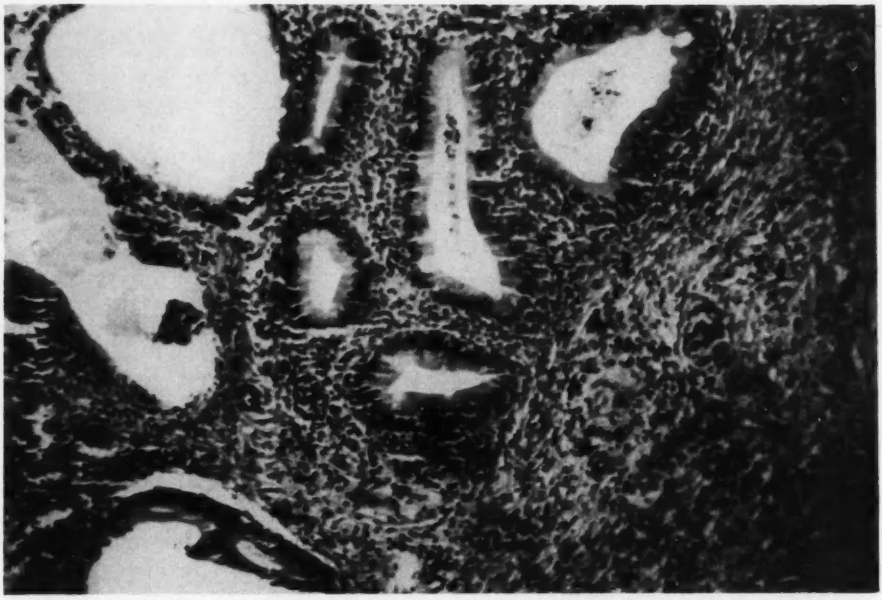

FIG. 5. Case 5. Actively secreting, single-layered columnar epithelium of "intestinal type."

tissue was seen in the form of an iris contracture of the vesical neck. Transurethral resection of the vesical neck was carried out. Postoperatively, the patient did well and within eighteen months the urine was sterile and she had no urinary complaints.

On histologic examination (fig. 6) the surface epithelium showed pronounced squamous metaplasia and in several areas beneath the surface of the epithelium small glandular elements were visible with a central lining of tall columnar epithelium with basal nuclei. There was a considerable amount of chronic inflammatory reaction and proliferation of connective tissue. There was also evidence of cystitis cystica which again was involved by squamous changes in the epithelium. The pathologic diagnosis was chronic cystitis with squamous metaplasia and cystitis glandularis.

Case 7. A white man, 34 years old, entered the Johns Hopkins Hospital on January 29, 1957 because of the cystoscopic findings of another urologist. The patient had no urinary symptoms and was being studied because of pain in the right upper abdominal quadrant. Intravenous urograms disclosed obstruction at the left ureteropelvic junction with a small stone. After cystoscopy, performed elsewhere, the patient was told that he had a large cyst in the bladder.

On general physical examination no abnormalities were detected. Phenolsulfonphthalein was 55 per cent in one hour; results of urinalysis were normal. The intravenous pyelogram showed moderate hydronephrosis on the left from obstruction of the ureteropelvic junction and a 1 cm. stone in the lower calyx.

Cystoscopy disclosed an irregular mass about 1.5 cm. in diameter arising from the region of the left ureteral orifice. The vesical mucosa surrounding this had a cobblestone appearance and several small cysts were visible. This process involved the entire trigone and extended approximately half way up the posterior bladder wall and for a lesser degree of the lateral walls. The dome and anterior wall of the bladder were normal.

Transurethral resection and bimanual examination were carried out with use of a general anesthetic. The large mass of tissue was removed down to normal appearing muscle and biopsy of several other areas around the trigone and posterior bladder wall was performed be-

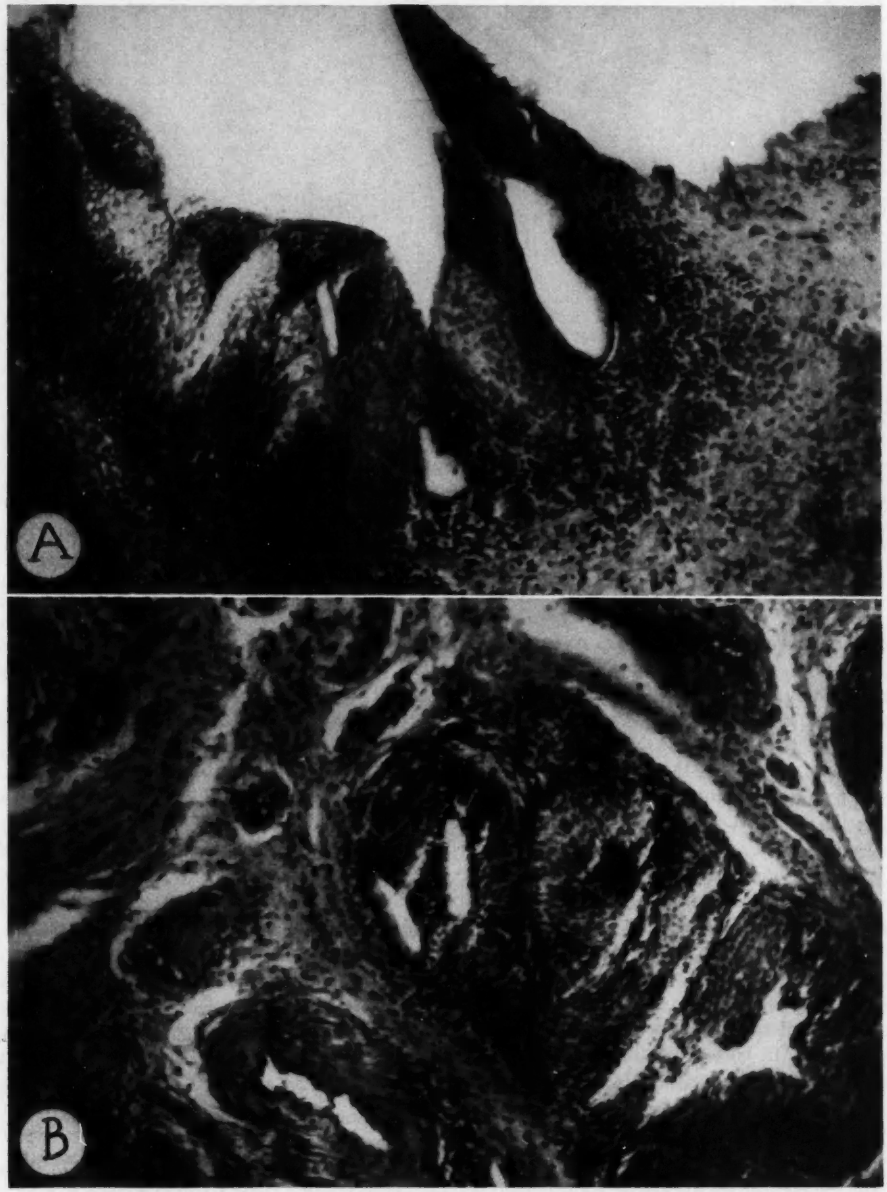

FIG. 6. Case 6. *A* shows severe squamous metaplasia of surface epithelium with two glandular spaces lined with columnar epithelium. *B* shows another such lesion with columnar epithelium arising from a squamous cell type.

cause of a question of a possible malignant lesion in the pathologic report.

The patient was returned to the operating room five days later and suprapubic loop resection of the entire floor of the bladder was carried out and several more adequate biopsies from the posterior bladder wall were performed. Deep muscle layers in the region of the base of the intravesical mass were also obtained. These sections showed essentially the same histologic

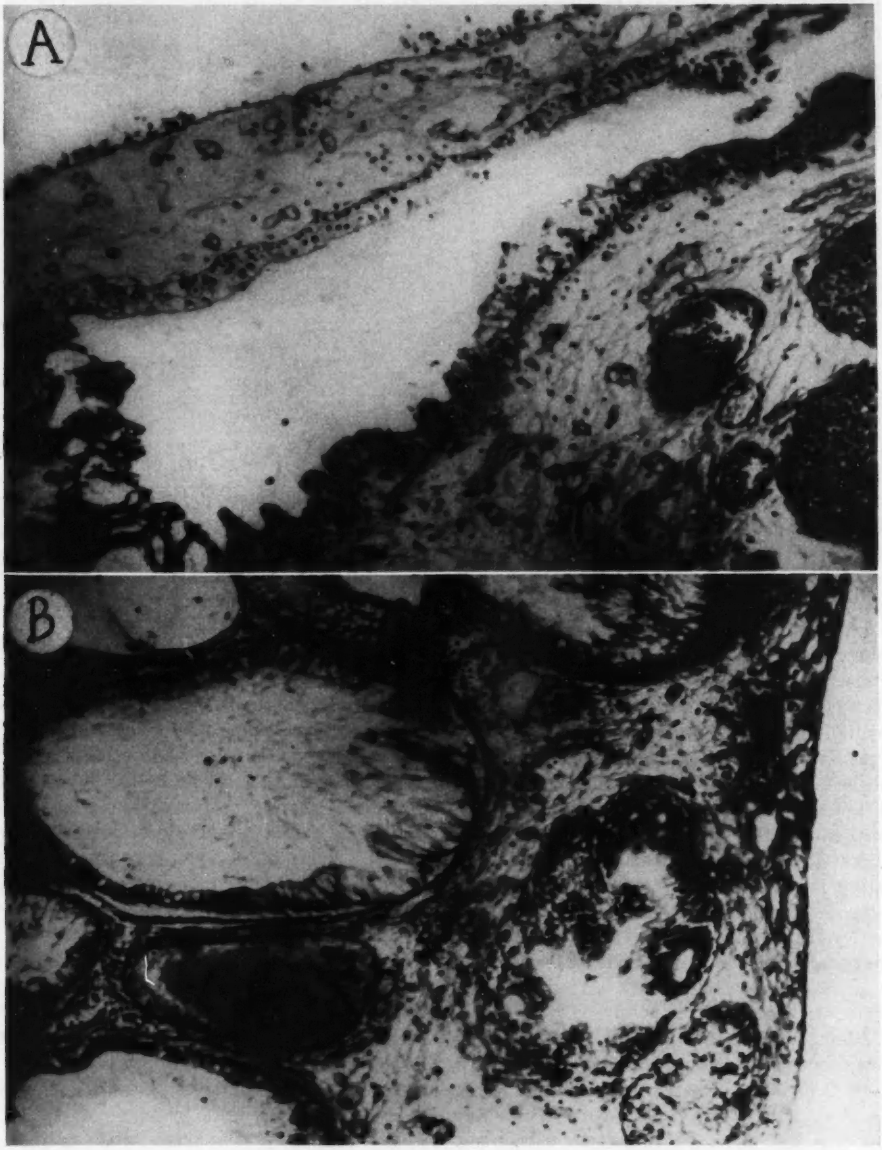

FIG. 7. Case 7. Stages of glandular development. Variation from transitional to columnar type of epithelium is seen in *A*. Actively secreting "goblet" cells are seen in *B*. See figure 8.

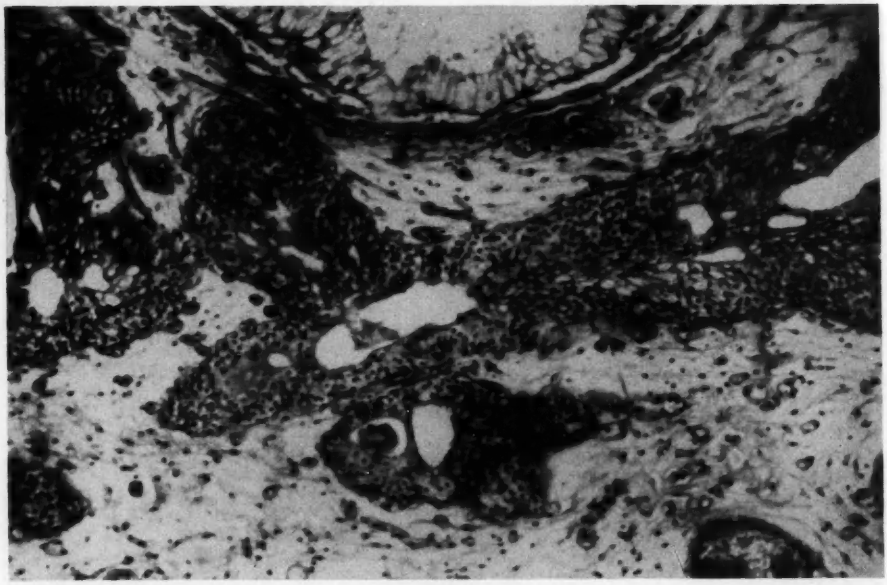

FIG. 8. Case 7. Variation from transitional to columnar type of epithelium. See figure 7.

picture as previously described without any evidence of deep muscle invasion. Periodic cystoscopic examinations have shown continued evidence of cystic change but no evidence toward neoplasia. The patient has continued to have a mild asymptomatic urinary infection.

On histologic examination (figs. 7 and 8) all sections showed small cystic areas lined by columnar cells which secreted a mucinous material. This epithelium appeared hyperplastic in places forming papillary projections into the lumens of the cysts. There were also cystic areas lined with what appeared to be normal transitional epithelium. There was also a vascularized stroma. There were a few areas that showed suggestive invasion of the most superficial layers of the bladder muscle. The pathologic diagnosis was cystitis cystica and cystitis glandularis, questionable mucus-forming adenocarcinoma.

DISCUSSION

Although this is a relatively small group of cases, several interesting observations can be made. Four of the 7 patients had normal urine. The three with grossly infected urine were the ones who had the most prominent symptoms, undoubtedly related primarily to the infection and not to the lesion under consideration. Two of the patients with normal urine had clinical evidence of prostatitis. In 2 patients, gross hematuria was a prominent symptom and one of these (case 3) had severe dysuria and infection. Painless bleeding was the only symptom in case 1. In case 4 the only presenting complaint was gradually progressive evidence of prostatism. Of particular interest is patient 7, who had absolutely no urinary symptoms and no abnormalities in the urine, the cystitis glandularis having been found incidentally during the course of thorough investigation of upper abdominal pain. This agrees with the other reported cases in that there is no symptom complex characteristic of glandular metaplasia in the urinary tract, and actually the only symptoms of note, except gross hematuria, are those secondary to infection or obstruction. In contrast to the cases reported by others, most cases herein reported were not associated with pyuria or symptoms of vesical irritability. This fact makes one wonder if chronic irritation of the vesical mucosa is actually necessary for development of a glandular type of metaplasia in the bladder.

The location of the change in the epithelium was variable, although in 5 cases it was primarily

at or near the trigone of the bladder. The change in one of the remaining cases was located on the posterior wall near the dome, and the other was on the posterior wall well away from the trigone. Of those lesions involving primarily the trigonal area, three showed the typical changes of cystitis cystica, consisting of cysts lined with normal-appearing transitional epithelium, and the glandular change seemed to involve the lining epithelium of these cysts. The epithelium was of a simple columnar variety without evidence of active secretion. In case 6, the findings were limited to the region of the vesical neck in a woman, and were associated with pronounced squamous metaplasia. The columnar epithelium was in close proximity to the squamous cells present in the walls of cysts. The best example of an actively secreting gland of an intestinal variety was seen to be confined primarily to the trigone, which is in variance to the observations of others who believe that this variety of metaplasia should occur elsewhere in the bladder. It is also interesting that the other racemose-gland type occurred in an area that was in communication with the colon. One may suggest that actually it was intestinal epithelium that was obtained at biopsy, but the tissue was obtained well away from the fistulous tract, and it is doubtful that the intestinal epithelium would grow from a site involved by severe inflammatory reaction and necrosis into an area of presumably normal transitional epithelium. Case 3 also presents an unusual situation in that glandular change is seen in a 4-year-old boy who had been in perfect health until the onset of a urinary infection. In this case, although the glandular changes are not as typical as most, they do not seem to be of the intestinal variety as one might expect, since the lesion was confined primarily to the fundus of the bladder. It should be mentioned that there was no evidence of any urachal abnormality in this child. It is also difficult to explain the calcification in this case, since the symptoms were of relatively short duration.

Typical changes of cystitis cystica were evident in 4 cases and, in a fifth case, nests of cells of the squamous variety were prominent. This would seem to be of more than incidental interest, and we believe that in most cases occurrence of glandular structures in the bladder represents the metaplasia of the lining epithelium of cystitis cystica from a squamous or transitional-type to a columnar form. The fact that chronic inflammatory reaction is present microscopically, even in those cases without evidence of gross urinary infection, may represent the local response of tissues that are reacting to an altered environment, as is seen in association with neoplastic processes.

CONCLUSIONS

In most cases, glandular changes in transitional bladder epithelium represent a later stage of a metaplastic process involving the epithelium in the cysts of cystitis cystica. Columnar epithelium may arise from transitional or squamous epithelium and may be of a simple columnar type or an actively secreting type closely resembling intestinal columnar epithelium.

Although chronic irritation from infection, trauma, or obstruction may predispose to cystic and glandular metaplasia, these lesions may also occur in apparently otherwise healthy bladders.

There is no consistent correlation between the location of the metaplastic process and the predominant cell type of columnar epithelium in the glands of cystitis glandularis.

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THE INCIDENCE OF SEVERE REACTIONS FROM PRESENT DAY UROGRAPHIC CONTRAST MATERIALS: A REPORT ON DATA COLLECTED FROM MEMBERS OF THE ASSOCIATION

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All contrast media used for excretory pyelograms evoke undesirable side reactions in some patients. Many of these are mild and transient, such as flushing, feeling of warmth, metallic taste, arm pain, nausea and vomiting. The more serious side reactions include urticaria, asthma and shock and, on rare occasions, these result in death. Recently new compounds have been developed which consistently yield pyelograms of excellent quality and also appear to evoke fewer side reactions.

The purpose of the present study has been an attempt to determine whether these compounds are universally safe, and how free they are from serious reactions. Another purpose of the survey has been to find out the experience of representative North American urologists on the value of tests for predicting reactions, as well as to determine the prevalent attitude on the value of antihistamine drugs in their prevention.

A questionnaire was sent to all of the active members of the Association and the majority replied. The following tabulation enumerates the data that were reported:

Number Reporting	Medium	Number of Injections	Severe Reactions		Deaths
			Allergic	Shock	
41	Hypaque	111,000	150	117	1*
12	Miokon	20,500	13	15	0
10	Renografin	13,000	2	4	0
—			—	—	—
63		144,500	165	136	1

* This fatal reaction was reported by a member but the case was not seen in the hospitals from which he reported data.

The majority of the reporters expressed some degree of enthusiasm regarding lack of reactions that have occurred with the new agents, yet we see that there is about a 1 in 500 over-all incidence of severe reactions; and none of the compounds is free from this risk.

The death occurred in a case where 1 cc of the medium was introduced intravenously as a test and no reaction occurred. The final injection was given 45 minutes later and within five minutes the patient had a circulatory collapse. Oxygen, intravenous fluids, neosynephrin and finally cardiac massage by the open method was done. An authority in the field of allergy research[1] has informed me that this death probably was not due to an allergic or histamine release mechanism for the reason that no reaction of an allergic nature was evoked by the preliminary test dose. It was postulated that a saratonin or some other chemical release might have been the basis for the reaction and that it probably would not have been prevented by antihistamine premedication.

Our group reported deaths with other previously used media as follows:

Urokon	6 deaths
Diodrast	4 deaths
Neoiopax	1 death

There were 41 persons who reported the use of some test procedure for predicting sensitivity to the compounds. Many employ intradermal or conjunctival testing yet only 2 persons believe that these tests have any value at all. It appears that these tests are performed not so much for patient protection but rather for legal protection of the doctors. Pendergrass,[2] in a 1955 survey of 31 deaths from contrast media, reported that sensitivity tests were negative in three-fourths of the patients who died.

Many of our members inject 1 cc or less of the contrast medium as a test for reactions and the majority believe that this is a reliable indication. Yet there are 14 who point out that this is completely unreliable. The Pendergrass report indi-

[1] Sheldon, John M.: Personal communication.

[2] Pendergrass, E. P., Hodes, P. J., Tondreau, R. L., Powell, C. C. and Burdick, E. D.: Further consideration of deaths and unfavorable sequelae following the administration of contrast media in urography in the United States. Am. J. Roentgenol., **74:** 262–287, 1955.

cates that two of the fatal reactions occurred with less than 2 cc of the contrast medium.

The experiences of our members with antihistamine drugs for preventing reactions have been varied in regard to the results. Nearly every person who reported their use expressed a belief that they are distinctly valuable. Those who administer the drugs orally appear to be the least enthusiastic as a group; yet some of these have high praise for the method. It would appear that oral premedication has been most effective when employed in fairly large doses that are given at least an hour before the injection of the contrast medium. One member reported that he gives 100 mg. of pyribenzamine orally to all patients who have a history of allergy and that he has observed excellent and uniform protection from reactions in these patients.

Those who have employed antihistamine drugs intravenously have had better results in the aggregate than the men who have given them orally. There are two methods of administering the compounds intravenously. The method used most is to mix the antihistamine agent with the contrast medium for simultaneous injection. The other method is to give the antihistamine agent intravenously from 3 to 5 minutes before giving the iodine compound. Investigators in the field of allergy find that the latter type of procedure offers greater protection against histamine release than does the simultaneous injection; and clinical experience would appear to bear out that assertion. Our members who have given antihistamine drugs along with the injections of the contrast media have all found a lessened incidence of reactions but a few have made comments to the effect that reactions have occurred often enough to raise a doubt as to the value of the method. This experience is paralleled in the reports that have appeared in the literature where simultaneous injection techniques have been used.[2-9] However, there are several of our members who employ the simultaneous injection technique and have reported only occasional minor reactions.

There has been a unanimous agreement concerning the value of antihistamine protection among those persons who have administered the drugs intravenously as a premedication. The largest series reported was that of my own colleagues [10, 11] who have now employed 50 mg. benadryl intravenously as a premedication in approximately 3000 cases where 70 per cent urokon has been used. These patients have been observed at the Wayne County General Hospital under the supervision of Dr. Jack Lapides and only two allergic reactions occurred, and no shock reactions. One case of mild urticaria occurred and one of severe urticaria with bronchial spasm was relieved by adrenalin. One can only speculate upon the nature of reaction that might have occurred in this patient had not benadryl been competing for histamine that was released by the iodine compound. In this connection, some investigators [12, 13] believe that all anaphylactic or allergic reactions cannot be avoided by the administration of antihistamine drugs since it has been shown experimentally that maximum effective doses of these drugs do not completely eliminate the actions of injected histamine.

One reporter stated that he gives 10 mg. of chlor-trimeton intravenously as premedication to all patients who give a history of allergy and he has observed only one mild reaction in this group. Another has prescribed the same premedication for 600 patients who gave a history of allergy and only one had any reaction—a single hive.

Some of the lesser reactions such as nausea, vomiting and arm pain appear to be unaffected by benadryl or chlor-trimeton. Lapides compared

[3] Bohne, A. W. and Christeson, W. W.: Clinical evaluation of a concentrated iodine preparation. Radiology, **60:** 401–405, 1953.

[4] Getzoff, P. L.: Use of antihistamine drug prophylaxis diodrast reactions. J. Urol., **65:** 1139–1142, 1951.

[5] Moore, T. D. and Sanders, Nelson: Reaction to urographic agents with and without antihistamines. J. Urol., **70:** 538–544, 1953.

[6] Olsson, Olle: Antihistaminic drugs for inhibiting untoward reactions to injections of contrast medium. Acta radiol., **35:** 65–70, 1951.

[7] Simon, S. W., Berman, H. I. and Rosenblum, S. A.: Prevention of reactions in intravenous urography. J. Allergy, **25:** 395–399, 1954.

[8] Winter, C. C.: The value of chlor-trimeton in the prevention of immediate reactions to 70 per cent urokon. J. Urol., **74:** 416–421, 1955.

[9] Utz, David C. and Thompson, G. J.: Evaluation of contrast media for excretory urography. Proc. Staff Meet., Mayo Clin., **33:** 75–81, 1958.

[10] Lapides, Jack and Boyd, Robt. E.: The effect of benadryl in allaying allergic manifestations of 70 per cent urokon. J. Urol., **75:** 1016–1118, 1956.

[11] Lapides, Jack: Personal communication.

[12] Bersack, S. W. and Whitaker, T. E., Jr.: Effect of diphenhydramine (benadryl) on side-reactions in intravenous urography. A.M.A. Arch. Int. Med., **91:** 618–625, 1953.

[13] Wells, J. A., Morris, H. C. and Dragstedt, C. A.: Modification of anaphylaxis by benadryl. Proc. Soc. Exper. Biol. & Med., **61:** 101–106, 1946.

the incidence of these reactions in the 70 per cent urokon cases and found that nausea and vomiting occurred just as often in the premedicated patients as among those who had urokon alone.

At the University Hospital we have only recently begun a series of cases that are premedicated with phenergan, an antihistamine drug which has a profound anti-emetic property. Twelve milligrams of phenergan are administered about five minutes before the pyelographic medium is injected. Only 210 patients have been treated in this manner at the present time but there appears to have been a significant decrease in the occurrence of nausea and vomiting. The following tabulation indicates the observations made on a control series as well as the cases premedicated with phenergan:

	Cases	Allergic Reactions (Urticaria and Dyspnea)	Side Effects	
			Nausea	Vomiting
		per cent	*per cent*	*per cent*
Controls.....	364 Hypaque	3.1	13	2.2
No antihistamine.....	354 Miokon	2.0	22	3.7
12 mg. phenergan.....	134 Hypaque	0	4.5	0
Intravenous....	76 Miokon	0	6.5	1.3*

* 1 case.

A disadvantage of antihistamine administration is the soporific effect that sometimes occurs. Occasionally patients become quite sleepy when these drugs are administered by any route. This effect has no great disadvantage in the hospitalized patient but can be disturbing or even potentially dangerous to the ambulatory patient, particularly one who has driven in an automobile to the x-ray laboratory. When ambulatory patients are given these drugs they should be observed for a short period of time and if sleepy should be given amphetimine to counteract the somnolent effects—and should not drive a motor car for several hours.

The protective value of antihistamine drugs in patients who have had previous reactions has been demonstrated in but few reported cases. Olsen in 1951 reported on "a number of cases" who had previously experienced reactions to the same medium but when protected with 20 mg. benadryl they suffered no discomfort at all. This investigator expressed the opinion that 20 mg. benadryl administered intravenously is adequate protection against any amount or repeated injections of the medium.

A significant case in this category was reported to me recently by my colleague Dr. Melvin Figley in the Department of Roentgenology, who personally supervises all of the arteriography that is performed at the University of Michigan Hospital. He observed a shock reaction following arteriography with 70 per cent urokon in a young man who was examined for a vascular anomaly. A repeat arteriogram became necessary so 50 mg. benadryl was administered intravenously a few minutes before the urokon injection and no reaction occurred.

Another, similar experience occurred in a University student who had a severe allergic reaction following pyelography with hypaque. Later another pyelographic study was carried out with hypaque but this time intravenous premedication with 50 mg. benadryl was used and he had no reaction.

SUMMARY

This inquiry has revealed a great enthusiasm for the newer contrast media that are available today. These compounds evoke very few side reactions; in fact some urologists reported large series of cases in which there were no reactions of any sort; but these new compounds occasionally evoke serious reactions and one fatality has occurred.

The majority of our members use intradermal or conjunctival tests of sensitivity but have no faith in the tests except as a protection against legal action.

Many believe that a test dose of the contrast medium affords a good index of reaction susceptibility, but the experience of the group has demonstrated the unreliability of even this method of testing.

Antihistamine protection appears to be a reality and the most effective method appears to be the employment of intravenous premedication.

Authorities in the field of allergy research believe that most of the dangerous reactions that occur with pyelographic medium injection can be prevented by the proper use of antihistamine drugs. Whether all fatal reactions could be elim-

inated by this means can only be determined by the observance of an enormous number of cases. For it should be recalled that there were 31 deaths in over three million cases reported by Pendergrass in 1955; and our survey revealed one death in over 140 thousand cases. Yet prevention of serious reaction or death, no matter how rare the occurrence, should be the goal.

The members of this society could determine the ultimate value of antihistamine protection within the course of a year or two if a number of our group would agree to administer these drugs routinely and would report the occurrence of any adverse reactions. For only by obtaining records of an enormous number of cases can this important matter eventually be settled. It is my hope that our society might express a willingness to embark on such a worthwhile venture.

THE PERINEUM IN EPISPADIAS

R. H. FLOCKS AND D. CULP

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Our interest in the condition of the perineum in epispadias and vesical exstrophy with epispadias was aroused by the following experience:

A patient entered the hospital at the age of 12 in July 1956 with complete epispadias. The bladder capacity was somewhat smaller than normal. No sphincter control whatsoever had been present from birth. In 1951, the patient underwent repair for epispadias with incontinence according to Young's technique. This was not successful and resulted in scarring and fistula formation and continuous incontinence. He entered the hospital for further therapy.

Because of the marked scarring, it seemed obvious that nothing more could be accomplished by means of a secondary Young type of approach from the anterior abdominal side. It was therefore decided to divide the urethra just distal to the prostatic urethra and leave it attached to the bladder. Then this urethra would be displaced downward and connected to the skin some place in the perineum, possibly using the anal sphincter to aid in controlling the urine. Therefore, the patient was placed in the exaggerated lithotomy position and the classical incision for perineal prostatectomy made. To our surprise, it was found that the perineal musculature was well developed. After the anus, rectum and levator ani muscles were dissected free and the central tendon divided, it was easy to place a finger underneath the inferior border of the urogenital diaphragm and proceed by blunt dissection up to the neck of the bladder and region of the prostate. This was readily pulled down to the perineal area and brought into the perineal wound. The urogenital diaphragm was surprisingly thick-muscled; the transverse perineal, ischio and bulbocavernosus were well developed. These all met at a central raphe in the midline which was an upward extension of the central tendon. It was therefore decided to bring the bladder neck down to the lowermost portion of the cephalad surface of the urogenital diaphragm and bring a tube of skin through the urogenital diaphragm just above its inferior border. This placed the new membranous urethra in essentially its normal position and it was readily anastomosed to the prostatic urethra with interrupted fine catgut sutures. The new urethra emerged from the external surface of the urogenital diaphragm in almost the normal position in the midline just above the inferior or posterior border of the urogenital diaphragm. The skin was closed in the usual manner. Therefore the epispadias was converted to a perineal type of hypospadias. The patient has total continence and only slight urinary frequency. He is able to hold his urine completely for several hours. The bladder capacity is gradually increasing. The upper urinary tract has remained essentially normal. It is planned to construct a new urethra much like one would do in a case of true perineal hypospadias.

A review of the literature reveals few references to the condition of the perineum in epispadias. Special emphasis is made on the variability of the amount of musculature in the perineum, but an accurate description or photographs are not available. The diagram of Shultz shows the situation in the female where, with the development of the vagina, the situation is almost normal, while in marked degrees of exstrophy and epispadias, it may very well be that the entire musculature of the perineum is absent. In the majority of cases, however, there is a surprising amount of musculature as evidenced by the case just described by us, and a second patient in whom we carried out dissection of the perineal musculature (figs. 1 to 5). The good results of Marion, described in 1934, in which he utilized a stab wound through the perineum with a free skin graft for a urethra, would also seem to indicate that in his cases adequate musculature was present. It is also likely that the good results obtained by Young's technique were obtained in those instances in which the urethra was displaced posteriorly rather markedly, so that the musculature in the perineum could be utilized, much as we utilized it by the perineal exposure in the case described above.

One of the early descriptions of the pathological anatomy of bladder exstrophy was that of Samuel Shattock in the Transactions of Pathological Society of London, published in 1894. He empha-

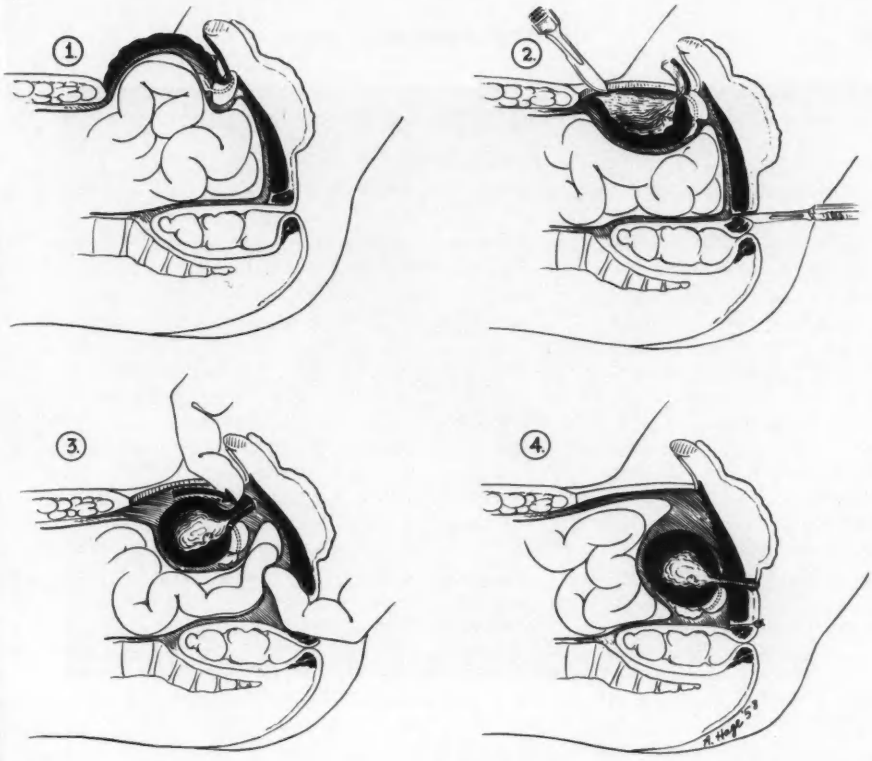

FIG. 1. Technique of converting exstrophy with epispadias to hypospadias. Illustrated also in figures 2 to 5 (patient R. H., GU 57-350).

1, Sagittal section shows exstrophy of bladder, epispadiac penis and muscular urogenital diaphragm. *2*, Dissecting bladder, urethra and prostate free from surrounding structures. Below, one is doing classical perineal approach to lower or inferior border of urogenital diaphragm. *3*, Bladder has been closed and urethra converted to tube. Inner surface of urogenital diaphragm is being separated from perineum to make bed for bladder. *4*, Bladder and prostate in new position, urethra having been drawn through muscular urogenital diaphragm and anastomosed to skin of perineum. Note that bladder, prostate and urethra are now in relatively normal position of perineal hypospadias.

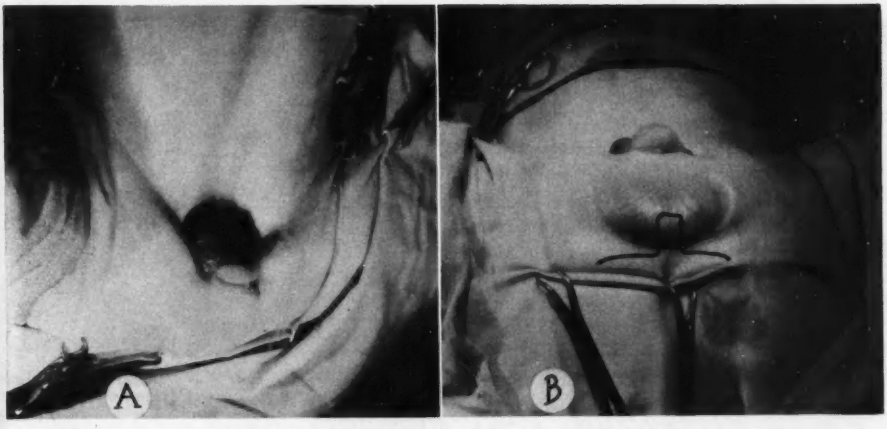

FIG. 2. *A*, appearance from above (4-year-old boy) with exstrophy and epispadias. *B*, appearance from perineal approach. Incision is outlined by continuous line. Note flap for construction of urethra.

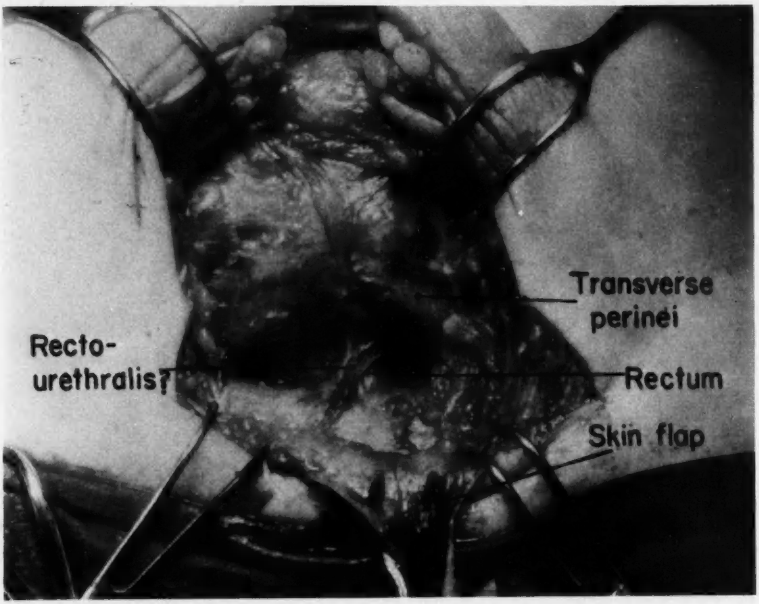

FIG. 3. Perineum has been exposed as for perineal prostatectomy. Note thick, muscular urogenital diaphragm.

sized the muscular attachments of the bladder on each side to the back of the pubic bones, and noted that if the pubic bones had been in normal position, these would correspond to the pubovesical muscles. He also describes (and this is the only such description I can find) the corpus spongiosum in exstrophy associated with epispadias. He states, "The full length of the corpora spongiosum from the bulb to the extremity of the glans is two inches. The corpus cavernosum is acutely bent in an S-shaped curve beyond its attachment to the pubic ramus. The corpora cavernosa are not fused." Arey describes the corpus spongiosum as arising from a fusion of two parts: one arising distally and including the glans penis, the other proximally from an area just distal to the true normally placed membranous urethra. In the two cases that we studied, no corpus spongiosum was found and this fact raises the question of its absence in these patients together with an absence of the entire bulbous portion of the urethra. The observations of Higgins would seem to indicate that the development of the perineum can be quite normal even though exstrophy is present, since he has described two patients in whom the penis, the urethra and the perineum

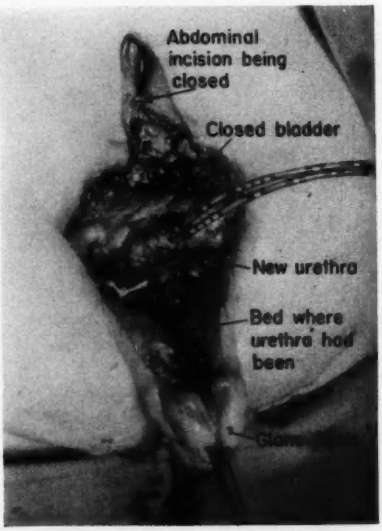

FIG. 4. Abdominal view. Bladder has been closed and urethra formed from urethral tissue along surface of epispadiac penis. Ureteral catheters serve as urethral splint.

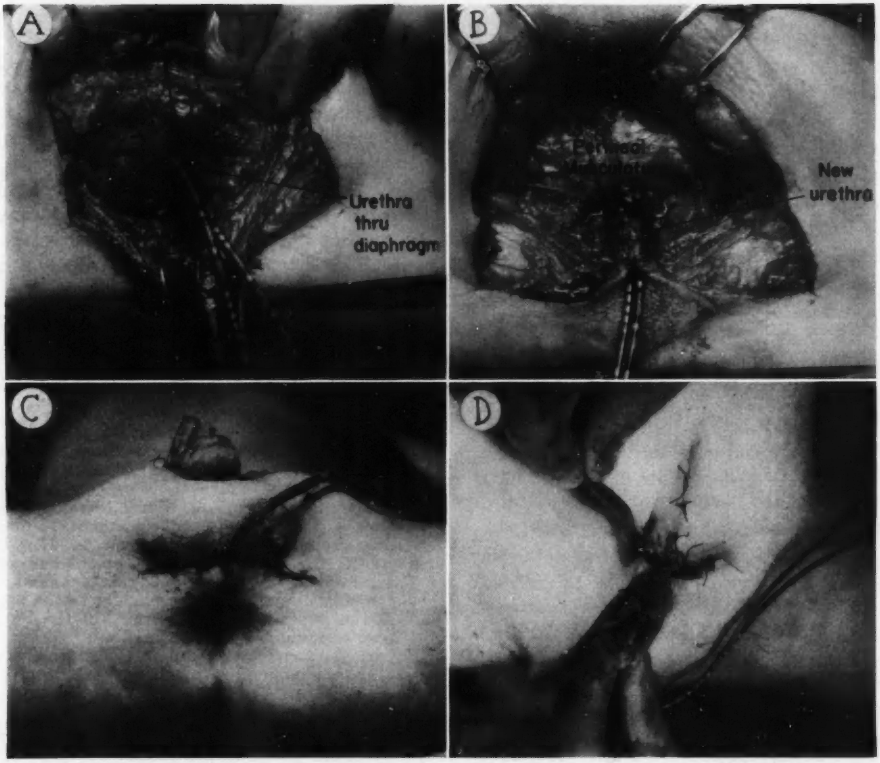

FIG. 5. *A*, perineal view. Urethra has been brought through urogenital diaphragm in its normal position. Note its relationship to transverse perineal muscles. *B*, perineal view continued. "Membranous" urethra sutured to skin flap to form perineal urethrostomy. *C*, perineal view. Wound closed. *D*, abdominal view. Wound closed.

seem to be normally formed although complete exstrophy is present. Trendelenburg first noted that bringing the symphyses together in their more normal positions seemed to re-create the muscular situation for continence, and this seems to be confirmed by the recent case report of Shultz. Marion was able to obtain continence of urine by performing a stab wound through the perineum and making a urethra from a free inlaid graft from the bladder to the skin of the perineum. This would indicate that muscle is present in the perineum. No description of this is given, however. Tracy Powell, without giving a description or illustrations of the anatomy, states that the urogenital diaphragm may be almost absent or may be almost normal with variations in between.

It would seem that an accurate assessment of the situation of the perineum in each patient would be of aid in the treatment of such cases, and in the understanding of the anomaly. For example, it is generally accepted that all the portion of the urogenital diaphragm above or anterior to the urethra is not developed in epispadias with separation of the symphysis, and that therefore the urethra is in its normal position. Is this necessarily true? In those cases with well developed urogenital diaphragms, may it not be that the defect is more a urethral imperfection than in the structure of the urogenital diaphragm? May not this be essentially the malposition of the prostate and bladder neck with absence of the membranous urethra, the bulbous urethra and the corpus spongiosum?

Figures 1 to 5 illustrate a dissection of the perineum in a patient with epispadias and exstrophy. They illustrate the technique for sepa-

rating the prostatic urethra from the glans penis, keeping the prostatic urethra and the bladder together, burying the bladder and making a tube out of the prostatic urethra which is then brought out perineally through the musculature in the urogenital diaphragm in its essentially normal position. There it is sutured to a tube of skin, thus creating a perineal hypospadias. This, in those cases in which the perineum is quite well formed, would seem to be the ideal type of operative procedure for burying the bladder in exstrophy. Reconstruction of a bulbous and anterior urethra and the shaft of the penis can then be accomplished at an adequate time if desirable and provided that the bladder capacity of the exstrophied bladder is ample. If this is very small and the musculature of the exstrophied bladder is poorly formed, other plastic procedures for enlargement of the bladder would be necessary to obtain continence and an adequate result.

SUMMARY

It would seem that there are marked variations of the structure of the perineum associated with epispadias and incontinence.

Not infrequently, however, the perineum is a strong muscular structure and its appearance suggests the possibility of a primary malposition of the prostatic and membranous urethras in the male, rather than an absence or primary malformation of the structures anterior to the membranous urethra.

The extent of absence or of malformation of the bulbous urethra and corpus spongiosum in males with epispadias needs further elucidation.

A possible operative procedure for epispadias with incontinence performed in two cases utilizing the muscular perineum is described. Continence was obtained in the patient without exstrophy and with an adequate bladder. In the patient with a small exstrophied bladder, although good abdominal closure and position of the bladder and prostatic urethra were obtained, incontinence persisted. This is possibly due to an extremely small bladder capacity in this patient.

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DISCUSSION

DR. JUSTIN CORDONNIER (St. Louis, Mo.): About two weeks after we had sent in our questionnaire to Dr. Nesbit, we had a death from miokon which I think should be reported. This was in a patient who was not particularly a good risk nor, on the other hand, a bad risk.

Following the usual procedure, 1 cc was given, and after a five minute interval 3 cc more were given. The patient went into a shock-like reaction from which he never recovered. At autopsy a myocardial weakness was found.

I am not sure that these deaths from contrast media we have had (and we have had at least three that I can recall), all of which have been reported with the exception of the last one, are on an allergic basis. I think some toxic factor is involved, and as far as I am concerned I rather doubt that benadryl is going to protect them, although I hope it will.

DR. EDWARD CAMPBELL (Philadelphia, Pa.): I should like to call your attention to an article which has been accepted for publication by the JOURNAL OF UROLOGY, on cystitis glandularis, by Shaw, Gislason and Imbriglia.*

We feel that for the first time this study and case presentation conclusively show a transition from cystitis glandularis to adenocarcinoma.

DR. REED M. NESBIT (Ann Arbor, Mich.): In connection with the paper on cystitis glandularis, I would like to ask Dr. McDonald, who has done a great deal of work on the experimental production of neoplasms of the bladder, whether he has observed in his animals a stage in which this type of tissue reaction is seen before the neoplasm is manifested.

Would you care to discuss that, Dr. McDonald?

DR. DONALD F. MCDONALD (Seattle, Wash.): It is very simple. In dogs we got tumors. In rabbits which did not get tumors we got cystitis glandularis. There was no stage in between.

PRESIDENT CAHILL: That is the first advantage of a carnivorous animal over a vegetarian. (Laughter)

DR. LUIS A. SANJURJO (Puerto Rico): I have had the opportunity to follow two patients lately, one of them referred to me by Dr. Dodson. The patient is a woman whose kidney had been removed for papillary tumor of the left kidney. She developed implants in the ureter, and we had to do a ureterectomy plus resection of the bladder. Several small stones also were fulgurated in the bladder.

I have been following this woman for the past seven months, doing monthly cystoscopic examinations. I could predict by looking at her bladder mucosa that a tumor was going to appear. It reached the point that at the time I removed up to six and seven small tumors which were proven histologically to be papillary transitional carcinoma.

During the last two cystoscopic examinations this pattern in the bladder mucosa of the cystitis glandularis or the vessels thrown into whorls has completely disappeared, and she has not had any further tumor.

Two months ago I had a patient who had vesical irritability. She had cystitis glandularis. I picked up a small snip biopsy of one of the lesions. The pathologist reported completely normal mucosa, but underneath that area there were innumerable mitoses. He could not state whether it was tumor or not. I repeated cystoscopy a month later, and the patient definitely had a papillary lesion, transitional scirrhous carcinoma.

DR. WILLIAM H. BOYCE (Winston-Salem, N. C.): These very beautiful sections by Drs. Brannan and Kittredge illustrate the changes that occur in cystitis glandularis.

In the course of several years of biopsies and histochemical studies of the urinary tract in various diseases, five patients with cystitis glandularis were encountered.

[Slide] This slide is taken from a renal pelvis that is hydronephrotic due to congenital ureteropelvic obstruction. There was no infection but a proliferation of the epithelium has occurred. The section is PAS treated but lightly counterstained with Weigert's method because there is practically no PAS-positive material in the epithelium. This finding is quite similar to that of the normal urinary epithelium.

[Slide] This is a section of epithelium with changes characteristic of cystitis glandularis, particularly those cases in which cystic changes develop. There is a marked increase in the intracellular PAS positive material of the tall columnar-like epithelium. In those cells nearest

* J. Urol., **79:** 815–822, 1958.

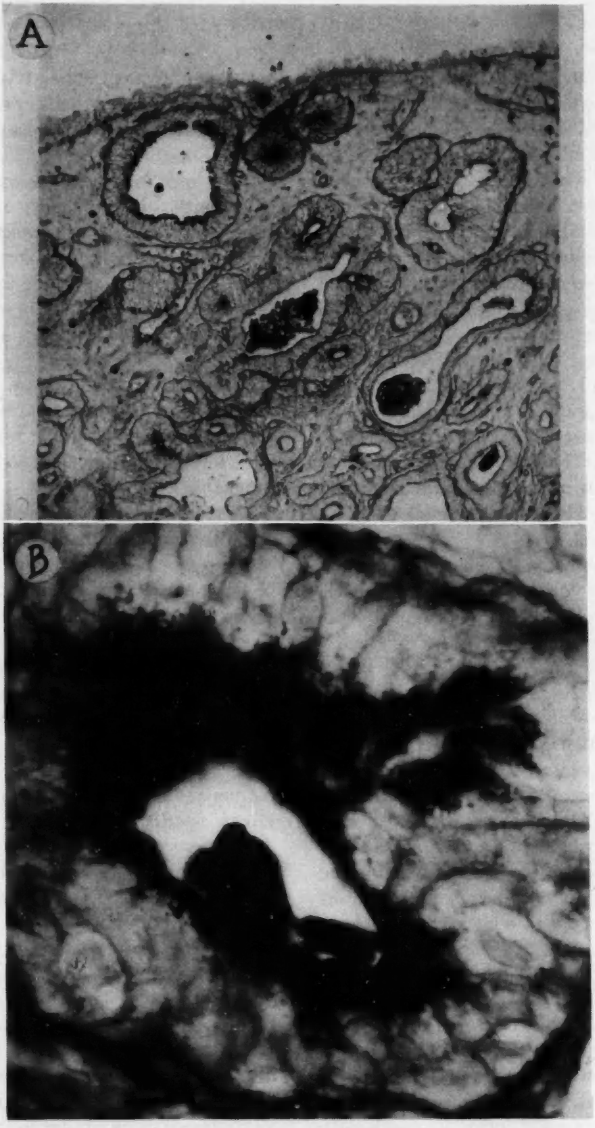

FIG. 1. Photomicrograph of cystitis glandularis, PAS treatment only

A, ×100. Amorphous material in crypts is strongly PAS positive (black). Deeply staining material lining surface of crypts represents intracellular PAS positive material. PAS positive material along basement membranes is extracellular.

B, same as *A*, ×1350. Basement membrane contains some extracellular PAS positive material, but adjacent cells contain few cytoplasmic granules. Cells lining crypt contain large quantities of PAS positive cytoplasmic granules. One pair of cells appears on verge of being sloughed into crypt.

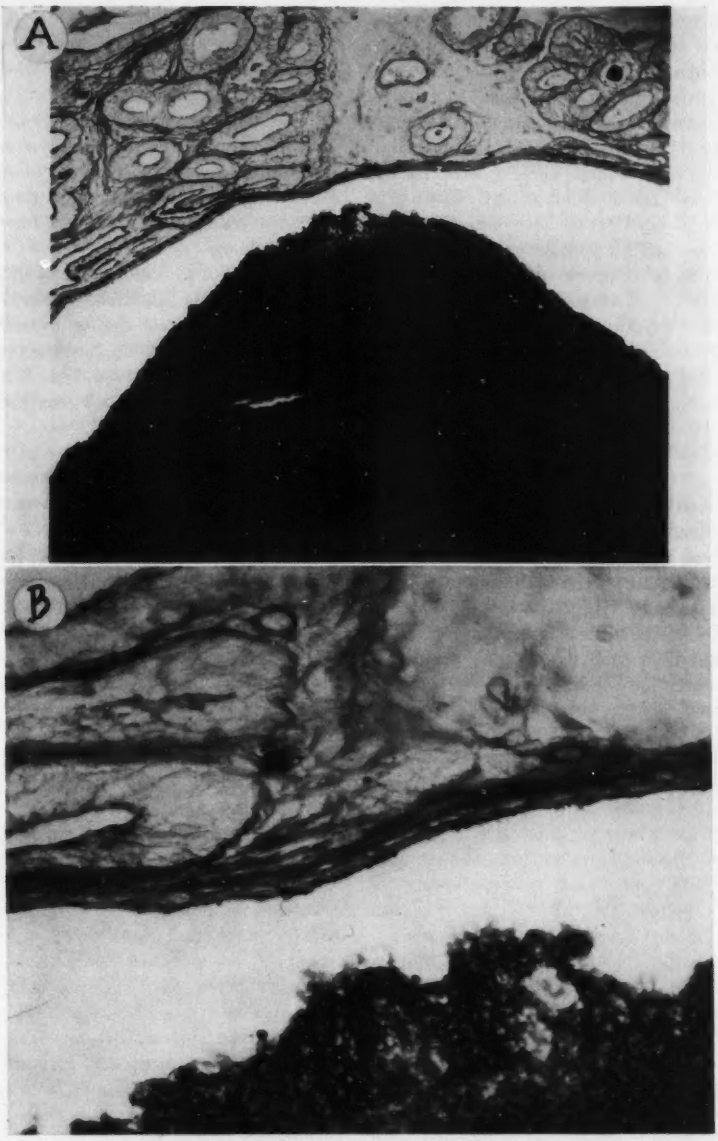

FIG. 2. Photomicrograph of cystitis glandularis (cystica), PAS treatment only

A, ×100. PAS positive material appears as amorphous black substance filling cyst cavity 2 mm. in diameter. Adjacent glandular crypts contain variable amounts of PAS positive material.

B, same as *A*, ×570. Margin of cyst is lined by a single layer of flattened epithelium containing little intracellular PAS positive material.

the basement membrane there is only a sparse stippling of small PAS-positive cytoplasmic granules. As one progresses toward the more superficial cells these PAS granules increase in number until the surface layer seems filled to bursting with solid masses of deeply positive PAS staining material (fig. 1). In the larger cysts the epithelium is often reduced to a single layer of flattened epithelial cells but the contents of the cysts are an amorphous mass of PAS-positive material (fig. 2). Such increases in PAS-positive cytoplasmic granules appear to be common to the increased "secretory activity" of transitional epithelium. We have obtained a positive correlation between the amount of uromucoid (insoluble carbohydrate-protein) in the urine and the amount of PAS-positive secretory granules of the transitional epithelium from patients with pyelonephritis, renal calculi, and primary closure of exstrophy of the bladder.

We may find that this presumably inert urinary epithelium has a great variety of enzymatic activity and can undergo changes from basic transitional to a secretory type of epithelium.

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): I would like to draw attention to the fact that brilliant men such as Dr. Boyce and Dr. Robert Kelley, whose slides I showed in my presentation, were men whom Dr. Samuel A. Vest was responsible for having inspired and trained.

DR. W. E. KITTREDGE (New Orleans, La.): In connection with the question whether cystitis glandularis is a precursor of cancer, I can say that in the small group that Dr. Brannan has presented to you we have not as yet seen malignancy develop in any of these cases. Some of them are recent, of course, but several of them go back at least ten years, and so far there has been no malignant change.

I would like to add a word of caution in connection with the handling of these lesions surgically. This concerns the use of the resectoscope loop in cutting into them, because they often contain large venous sinuses and can bleed more profusely than almost any other lesion I have ever seen.

I have learned from experience that although one naturally needs a good biopsy, when it comes to the actual treatment or removal of the lesion, coagulation is safer than cutting.

DR. RUBIN FLOCKS (Iowa City, Iowa): I would like to make it clear that the second case, the patient with exstrophy of whom we showed slides, remained completely incontinent, either due to the failure of the musculature of the perineum or the small size of the bladder.

UROSCOPY: THE CLINICAL LABORATORY OF THE PAST

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"Uroscopy," a word of Greek origin, means visual examination of the urine. To the medieval European the term implied much more than looking; it referred to a whole system of medical diagnosis and prognosis. It sometimes meant a test used to detect pregnancy or a means of divination and prophecy. The uroscopic scene was widely depicted in art and to a lesser extent in literature.

The procedure of uroscopy consisted essentially of visual inspection of the urine in a transparent container. The odor was sometimes noted, and occasionally the taste as well. The sweet taste of diabetic urine was known to the ancients as well as later physicians. However, such additional tests were strictly secondary.

Proper equipment for uroscopic examination was the matula, a transparent glass jar having a wide lipped mouth and a rounded body, intended to copy the shape of the bladder. It was carried in a cylindrical wicker basket just wide and deep enough to hold it upright, with a hinged cover of the same material. Both of these articles figure prominently in the art and illustration of medieval and renaissance times.

Uroscopic examination of the urine was the principal and often the only clinical test used in ancient and medieval medicine. As such, it was the equivalent of our present day extensive clinical laboratory procedures. In some cases, the other excreta such as the stool and vomitus were also observed and their characteristics noted, but most often no other test was done.

In medieval times there were periods when the examination of urine was the sole method of diagnosis. So great was the reliance placed on this test that it was thought unnecessary even to see the patient; since all important clinical changes would be reflected or mirrored in the urine if one only knew what to look for and how to interpret what he saw. The use of uroscopy as a major diagnostic procedure persisted until the early 19th century. As clinical chemistry and diagnosis advanced, uroscopy was used less and less by the ablest physicians, and finally only by quacks and irregular practitioners.

Gross inspection of the urine is still useful to the clinician although at the present time it is used almost solely by urologists. However, examination of the urine in one way or another has always played an important part in medical diagnosis from the most ancient times till the present.

While there are occasional references to the appearance of the urine in the ancient Egyptian, Babylonian and Sanskrit records, the first important descriptions are found in the Hippocratic writings (approximately 400 B.C.). These are much more rational than many later ones. Besides mentioning the appearance of the urine, note is made of the other circumstances such as the amount passed over a given period of time, the mode of passing, and any accompanying symptoms.

Thus, to quote from the Prognostics, "The urine is best which forms a whitish precipitate, simple and homogeneous throughout all the time of the sickness up until the crisis, and it indicates absence of danger and shortness of the illness. If the urine varies from this, the illness will be long and a happy outcome is less sure." "Clouds which float in the urine if white, augur well, if black, augur ill" and so forth.

The appearance of the urine is held to be of great diagnostic and prognostic significance not only in diseases of the urinary tract itself, but also in general diseases, particularly the febrile conditions which were then so common. The following are quotations regarding urinary disease: "A spontaneous passage of blood indicates a rupture of a small vein in the kidneys." "If a sick man passes urine with blood and sediment and is troubled with stranguary, it is a sign that he has some disease of the wall of the bladder." "To regularly urinate blood or pus indicates ulceration of the kidney or the bladder." "Those whose urine deposits sand have a calculus in the bladder."

In general diseases, the appearance of the urine was chiefly valuable as a prognostic sign of crisis, cure, or impending death. To quote: "The urine, having during a fever a white uniform sediment indicates a prompt resolution." "Urine a little red and having a slightly red and uniform sediment presages resolution on the seventh day." Among

urines which indicate danger in acute illnesses are urines of a bilious color—and urine variable in color and in sediment. Very unfortunate are urines with a black sediment.

Thus we see that Hippocrates and the Hippocratic writers were excellent observers and tried to relate their observations on the urine to the clinical situation of the patient. While we cannot always confirm the relationships which they saw, we detect a rational attempt to understand the significance of the various appearances of the urine. Many statements are contradictory and very possibly texts are corrupted, but these do not detract from their value.

After Hippocrates, there seems to have been little change or improvement in the standards of uroscopic diagnosis. No important or notable references are found until the time of Galen (approximately 130 A.D.). Even what Galen wrote about the urine was drawn mainly from Hippocrates, but he added a few important notations of his own. Speaking of pus in the urine, he wrote: "If it escapes alone and without the urine, this proves that the separation is occurring in the bladder itself. If the pus in entirely mixed, it comes from higher." Also, "A sign of an ulceration is the expulsion in the urine of a false-membrane."

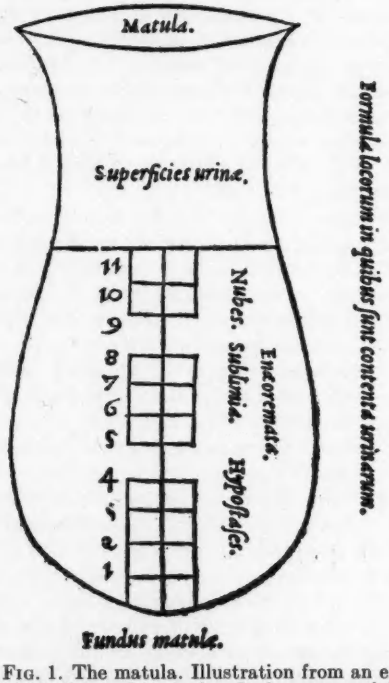

FIG. 1. The matula. Illustration from an early printed edition of Actuarius. It shows several divisions for detailed location of abnormal characteristics.

After Galen, for 500 years, there were no advances made. A compilation was made by Paulus Aeginata (625 A.D.) but it merely repeated the ideas of the Hippocratic writings and of Galen. A number of manuscript urine tracts attributed to Galen have survived from early and medieval times but are now generally referred to as "pseudo-Galenic." The urine tract of Theophilus Protospatharios who lived in Byzantium in the seventh century was important chiefly as the basis for many Arabic texts and for that of Actuarius some 600 years later.

Johannes Actuarius, the son of Zacharias, who died about 1283, was physician at the Byzantine court of Adronicus III Paleologus, emperor of the Eastern empire. He was the most important writer of the medieval period on uroscopy. His work was entitled "Seven Books on the Urine" (Peri Ouron or De Urina-Libri Septem). As mentioned above, he based his work on preceding authors. He was the first to describe the graduated matula (fig. 1) with eleven vertical divisions divided into three general regions. He gave minute descriptions of variations in color as well as differences in clarity, sediment, presence of cloudiness, surface scum, bubbles, etc. The causes of all these variations were explained on the basis of humoral theory. This work of Actuarius was widely recopied in manuscript in the original Greek. It was translated into Latin in the 15th century (fig. 2) and was among the earliest printed books on the urine. Many of the editions have appended at the end dissertations by Aristotle and by others on different varieties of color.

The works of the Arabian physicians merely repeated the opinions of Hippocrates, Galen, and the other ancient writers without significant changes. The school of Salerno, the first medical school in western Europe, derived its medical ideas from the ancients through the Arabian translators, and, as might be expected, uroscopy was of major importance. Examinations of the urine and the pulse were the mainstays of Salernitan diagnosis. The most famous early representatives, Constantinus Africanus (1018–1085), one of the founders of the school, and Bernard Gordon of Montpelier (1285–1318) both gave first place in their scheme of relative importance

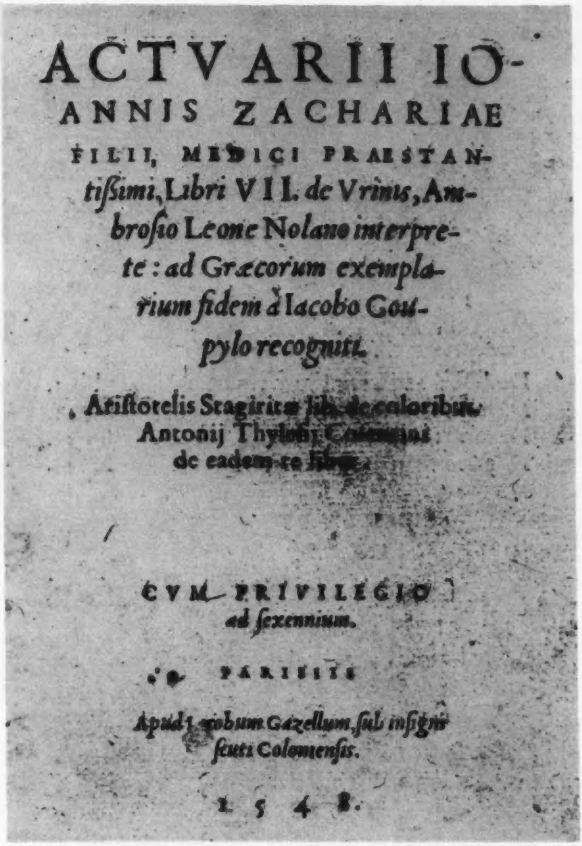
ACTVARII IO-
ANNIS ZACHARIAE
FILII, MEDICI PRAESTAN-
tissimi, Libri VII. de Vrinis, Am-
brosio Leone Nolano interpre-
te: ad Græcorum exempla-
rium fidem à Iacobo Gou-
pylo recogniti.
Aristotelis Stagiritæ lib. de coloribus.
Antonij Thylesij Colentini
de eadem re liber.
CVM PRIVILEGIO
ad sexennium.
PARISIIS
Apud Iacobum Gazellum, sub insigni
scuti Colonensis.
1548.

FIG. 2. Title page of a 1548 Paris Latin edition of Johannes Actuarius' book on urine.

to examination of the urine and second place to examination of the pulse.

The most famous Salernitan work is that of Gilles de Corbeil (died about 1220) a graduate of Salerno in the early 12th century, who was physician to Phillipe Auguste of France. His "Liber de Urinis" was a long Latin poem on uroscopy which was copied and memorized and reprinted for hundreds of years. It is very completely discussed by C. Vieillard, who in 1903 wrote a book on uroscopy, the last portion of which is devoted to a discussion of Gilles' work.

One of the best known of the early printed works was the section on urines of the Fasciculo de Medecina of Johannes de Ketham (Hans von Kircheim) who died about 1460. The table of urine glasses in his book describes 21 colors and their significance, with corner medallions explaining the four humoral natures or habits and indications of their relation to the various urinary appearances (fig. 3). This work was widely distributed, printed in several languages, and a beautiful facsimile was published by Lier in Venice, in 1925.

The uroscopic treatises became more elaborate in detail. About twenty different colors were recognized and when each one was considered with the multiple varieties of sediment, clouds, superficial changes, etc. the mathematical possibilities by geometric progression became truly huge in number. Attempts were made to tabulate and codify all these varieties and presumably by comparing the uroscopic findings with the tables the diagnosis became almost automatic. All the de-

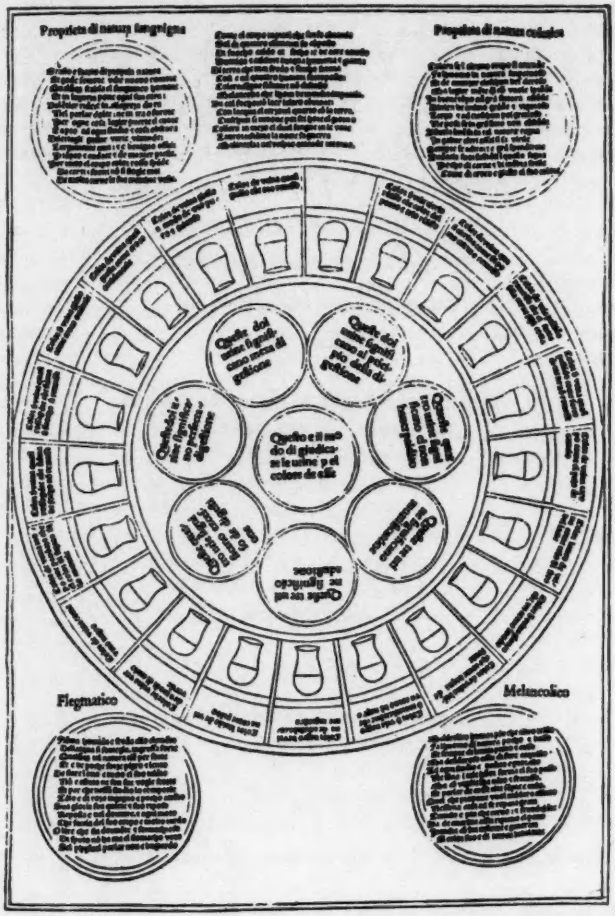

FIG. 3. Illustration of circle of urine glasses from 1493 edition of Johannes de Ketham's Fasciculus Medicinae. Outlined urine glasses were intended to be colored by hand. Inside circle, medallions tell of state of digestion accompanying color changes. Large medallions in corners outside circle enumerate characteristic properties of four major physiological states according to humoral theory.

scriptions and explanations in the books of this period were taken from preceding works and were of course based on humoral physiology and pathology. Treatment recommended was then of course directed to re-establishing the normal humoral balance.

Many of these urine tracts, large and small, were printed and circulated in the late 15th and early 16th century; one by D. Iodocus Wilichius in 1582 was probably the high point of this type of work. The colors were named in four languages and the book has literally dozens of outlines of urine glasses which were meant to be colored in by hand. A number of later texts were very popular, such as that of Davach da la Riviere, called "Le Miroir des Urines" which went through many editions in French in the 18th century, but they all were merely copies and re-arrangements of previous works.

From the middle of the 16th century on, most of the advanced physicians came to depend to a greater extent on accurate history and careful examination of the entire patient, rather than on the uroscopic examination or on uroscopic and pulse examination only.

Chemistry began slowly to emerge from al-

chemy during this period and attempts were made to analyze the urine. The first attempts by Paracelsus (1493–1541) might be called alchemical rather than truly chemical. In his scheme, mercury, sulphur, and salt replaced the four humors as being the basis of physiological activity, but the resulting physiology was just about as crude as the humoral. He attempted ineffectively to analyze the urine by distillation but most of all he castigated the older physicians and their ideas.

A much more accurate and rational attempt was made by Thomas Willis (1621–75), whose work "A Dissertation on the Urine" was published in 1674. He attempted a real chemical analysis according to the knowledge of the day and determined that the urine was composed of alcohol, sulphur, salts, spirit of urine, and earth. Crude as it was, it was a true beginning to the accurate study and chemical analysis of the urine which continued and progressed from that time on.

Uroscopy, as it had been previously practiced, became gradually outmoded and discredited, but did not drop from sight by any means. It continued to be used for more than 200 years longer by physicians of the old school, many of whom were sincere, but ignorant and poorly trained; also, it

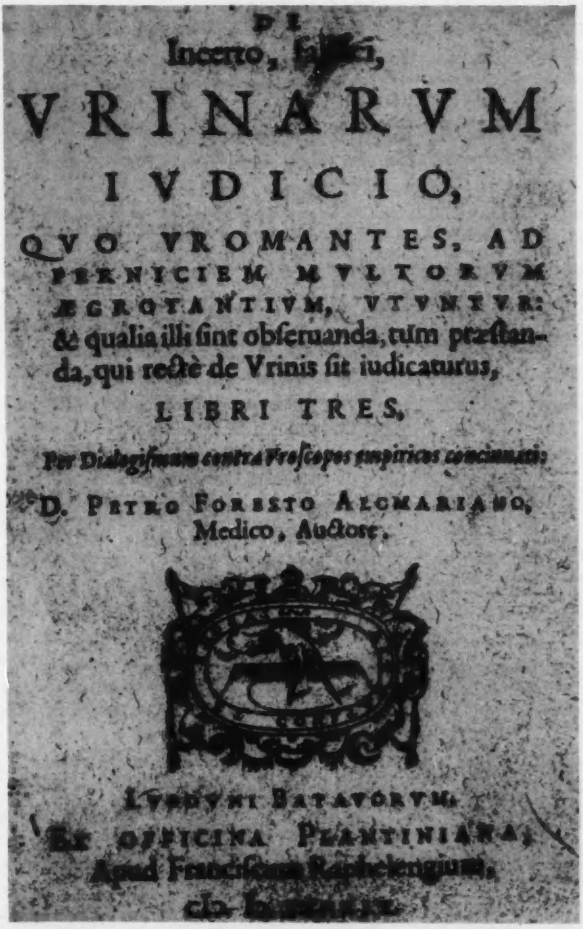
DE
Incerto, falsi,
VRINARVM
IVDICIO,
QVO VROMANTES, AD
PERNICIEM MVLTORVM
ÆGROTANTIVM, VTVNTVR:
& qualia illi sint obseruanda, tum præstanda, qui rectè de Vrinis sit iudicaturus,
LIBRI TRES,
Per Dialogismum contra Præcipes empiricos concinnati:
D. PETRO FORESTO ALCMARIANO, Medico, Auctore.
LVGDVNI BATAVORVM,
EX OFFICINA PLANTINIANA,
Apud Franciscum Raphelengium,

FIG. 4. Title page of 1589 Leyden edition of Petrus Forestus. This was first major work questioning value of uroscopy as means of diagnosis.

continued to be used by quacks, mountebanks and amateurs of all sorts, vulgarly called "water casters" or "piss prophets." The old texts continued to be reprinted in new editions and copied and rearranged under new titles.

During the 17th century, as the old procedure of uroscopy continued to lose favor with the best educated element of the medical profession, it came to be identified almost entirely with the irregular practioners. One of the first and most important critical publications appeared in Leyden in 1589 (fig. 4), written by Petrus Forestus (1522–97) a Dutchman. His title is self explanatory. In Latin "De Incerto, Fallaci Urinarum Iudicii—Libri tres—Quo Uromantes ad Pernicium Multorum Aegrotantum Utuntur: etc. (On the Uncertainty and Falsity of Judging Urine, as Uromancers, to the Harm of Many Sick People Do, etc.).

Somewhat earlier Thomas Linacre (1460–1524), a founder of the Royal College of Physicians in England, formulated a statute to forbid apothecaries taking urine specimens to physicians and then selling medicines on the basis of the physician's diagnosis. Later he formulated a second statute to prevent the doctors from prescribing on the basis of urine examination only. This measure was loudly opposed by the quacks, as we shall see later.

In a recorded instance, Dr. John Radcliff (1650–1714) at Oxford was asked to diagnosis a case on the appearance of the urine which was brought to him. He asked the occupation of the sick man. When told the man was a bootmaker

THE

PISSE-PROPHET,

OR,

CERTAINE PISSE-POT LECTURES.

Wherein are newly diſcovered the old fallacies, deceit, and jugling of the Piſſe-pot *Science, uſed by all thoſe* (whether *Quacks and* Empiricks, or other methodicall Phyſicians) who pretend knowledge of Diſeaſes, by the Urine, in giving judgement of the ſame.

By THO. BRIAN, M. P. lately in the Citie of *London*, and now in *Colcheſter* in ESSEX.

Never heretofore publiſhed by any man in the *Engliſh* Tongue.

Si populus vult decipi, decipiatur.

LONDON,

Printed by *E. P.* for *R. Thrale*, and are to be ſold at his ſhop at the ſigne of the Croſſe-Keyes, at *Pauls* gate.

1637.

FIG. 5. Title page of 1637 London edition of Thomas Brian

he took the urine specimen out and discarded it, filling the jar with his own. He then gave it back to the messenger and said that if the man would fit him with a pair of boots by examining his urine he would prescribe for the man in the same way.

The study of the irregular and lunatic fringe of medicine is always most entertaining, and in this subject it is no exception. There were many who with some medical training continued boldly to assert that they could diagnose all disease merely by examination of the urine. Some of these combined the examination of the urine with astrology, and casting the horoscope then became an essential part of the diagnostic procedure.

Merging with this group were those who were more properly called uromancers. These diviners claimed to see the future in the urine, just as others might see it in the lines of the hands, part of the hair, or the tea leaves in the cup.

Some of these charlatans had medical training or degrees, but many of them had merely learned by apprenticeship the rigamorole which they used. Many of them were merely what we would call traveling medicine men. The quack examined the urine and prescribed one or the other of his specific drugs, which was always just the thing for whatever ailed the patient. Of course, he moved on as soon as he had duped as many as he could.

Uroscopists and uromancers became the target of more and more ridicule of which a number of good examples have survived. One Thomas Brian published in London in 1637 a book entitled "The Pisse-Prophet" in which he ridiculed and scorned the uroscopists (fig. 5). A short while later John Collop in his "Poesis Rediviva" published in London in 1656 has a poem entitled "A Pisspot Prophet" in which the quack ironically berates the College of Physicians for forbidding diagnosis and treatment by uroscopy (the statute of Dr. Linacre mentioned previously).

"Have you a pain ith stomach? Yes, back and head?
Lord Master Doctor where have you this read?
I'th urine man; by this I ev'n can know
Each step, and stair by which to bed you go
Pisse takes the form of parts as it runs through,
I could no better know, was I in you
Hence looking-glasses, chamberpots we call
'Cause in your pisse we can discover all
Why this no less than Aaron's brestplate is
The seminalities of all ills in pisse
To trust in this the college doth forbid
Vile men would prelate-like have knowledge hid."

In this poem the uroscopist states the basis on which his diagnoses were made. It was known that the urine was drawn from the blood which in turn came from all parts of the body and it was thought that it picked up and carried with it the characteristics of all parts of the body and of their activities. The person who knew how to recognize these characteristic changes could discern them in the urine and thus make a diagnosis.

The uroscopists and uromancers were subject to more and more ridicule by playwrights, artists, cartoonists, caricaturists, and others. As usual, there were the stories of the ridiculous, for example, one quoted by von Hutten, who told of the physician who saw an oat grain in a glass of urine and deduced therefrom that the patient had eaten a horse.

Of course, a procedure so widely used could not

FIG. 6. Sculptured panel from Cathedral of Rouen, built in 13th century, shows physician seated at his lectern and examining flask of urine.

fail to be mentioned in literature. One of the oldest French fables, the Roman du Renart of the 13th century, tells of the king lion and the fox physician who examines the lion's urine to diagnose his illness. After observing it he tells the lion "a little longer and I should have been too late," and then prescribes for his illness.

Uroscopy is mentioned in Shakespeare on two or more occasions. One allusion is in Twelfth Night when Fabian is told to "carry the water to a wise woman," a second is in II Henry IV, Act 1, scene 3 when Falstaff says to the page "Sirra, you giant, what saies the doctor to my water?". The page replies, "he said, sir, the water it selfe was a good healthy water: but for the party that ow'd it, he might have more diseases than he knew for." Moliere, the famous French dramatist, is even more satirical in his treatment of doctors and uroscopists. In his "Le Medicin Volant" published about 1650, the doctor is depicted as a fool who goes on to drink the urine because, as he says, taste is a better judge than sight. Other cartoons and caricatures appeared at various times ridiculing the procedure itself and profession for using it.

It was in art that the procedure of uroscopy was most commonly depicted. For more than 500 years the person who was to be represented as a physician was invariably shown inspecting a urine glass. Often, the representation of the urine glass became a sign for a physician's home or office.

Probably the oldest known representation is a miniature in an illuminated initial of a 12th century manuscript of Maurus' "Traité de Urine." It typically shows the physician in his long robe examining the urine by holding the matula up to the light. This general idea is repeated over and over, and literally thousands of different representations are known in all media and from all eras since that time.

No aura of vulgarity or impropriety attached to the urine or its examination and there was no reluctance to use it in any milieu, even the religious. In sculptured panels from the library doors of the Cathedral of Rouen, built in the 13th century, two physicians are shown in uroscopic scenes

FIG. 7. Medieval sculptured chalice in Cathedral of Milan with small panel showing doctor in uroscopic scene. (From Desnos, Histoire d'Urologie.)

FIG. 8. Page from illuminated manuscript, Book of Hours of the Virgin, made in Luxemburg about 1430–1440. Shown in exhibit of Treasures of Morgan Library, New York City. Bespectacled and solemn rabbit physician is examining urine while his two patients, dogs on crutches and artificial legs, anxiously await his decision. Black and white copy cannot fully convey beauty of this brightly illuminated page.

(fig. 6). Also, the doors of the campanile of the cathedral of Florence, made by Pisano, include a panel with a uroscopic scene. A medieval ivory chalice in the cathedral of Milan is decorated with panels depicting several occupations, and that of the physician is, of course, a uroscopic scene (fig. 7).

Many manuscript devotional books were illuminated with uroscopic vignettes, some realistic, others whimiscal or humorous. Breviaries or Books of Hours, often show these scenes. One beautiful example by Jean Pucelle is that of Jeanne d' Evreux, Queen of Charles IV of France. It was made in 1325 and has two uroscopic scenes which can be seen in the facsimile published in 1957 by the Cloisters Division of the Metropolitan Museum of Art of New York. One hundred years later a book of Hours of the Virgin, now owned by the Morgan Library was illuminated (fig. 8). It shows a whimsical animal scene with a hare as the bespectacled doctor examining the urine of his patients who are dogs on crutches. This beautifully decorated page was reproduced in the Art Institute of Chicago Catalogue published for the exibit of the Morgan Collection in 1957. Another book of Hours is that of Anne de

Bretagne, published in 1508 and illuminated by Jean Bourdichon. It depicts Saints Cosmas and Damien and as usual one is depicted holding a urine glass while the other holds an apothecary jar.

Another type of art is represented by the work of the famous Itailan artist Andrea della Robbia (1437–1525) whose work in terracotta in so famous. A panel over the entrance of the hospital at Pistoia shows two monks, one examining the patient's pulse and the other examining his urine. The same artist's terracotta of an infant in swaddling clothes has been widely used as an emblem or coat of arms for orphanages and foundling homes. In a painting by Jean Gelle (died 1628 at Cologne) Christ is represented as a physician and, therefore, is examining a bottle of urine. The idea behind the painting is that the physician appears as a god to the seriously sick patient.

Probably the greatest number of uroscopic scenes were painted by the Flemish painters in the 16th and 17th centuries. Gerard Dou, Zorg, David Teniers, Von Ostadt, Ter Borsh, Netscher, Van Mieris and many others painted pictures depicting the uroscopist.

A special group which persisted long included those who claimed to be able to diagnose pregnancy by examination of the urine. An early accurate answer to this question has always been one of the most sought after in the medical field, and those who claim to be able to accomplish this never seem to lack for patients. Those who derided the uroscopists who diagnosed pregnancy by the urine would be most surprised to learn that in 1958 pregnancy can be diagnosed by the urine; not by the obviously sensible method of looking at it, but by the fantastic method of injecting it into animals. On the diagnosis of pregnancy many representations were satirical. Such were the much copied pictures by Smith and Gotfried Schalken (fig. 9) and Pieter Breughel also.

A favorite subject was the depiction of the "Mal d'Amour" from which large numbers

FIG. 9. Painting by Gotfreid Schalken (1643–1706) entitled "La Consultation Indiscrete." Theme of painting is diagnosis of pregnancy by uroscopy. Picture shows physician observing urine in which painter has faintly outlined a small figure signifying the embryo. Irate father sits at table scowling at his weeping daughter. Small boy smirking in background indicates by ancient sign that he is well aware of situation.

FIG. 10. Death and the Physician. From Totentanz series of Hans Holbein the Younger (1497–1543). Death in form of skeleton leads in the old man and presents his urine to physician as if to challenge physician's ability to help.

of the young women of the time suffered; due apparently to deprivation of male companionship. The doctor is usually represented examining the patient's urine although sometimes he is feeling the patient's pulse at the same time. In some of these, the general tone is slightly satirical or humorous, but more often serious.

Another branch of art in which this scene appears is in the Dance of Death (Totentanz or Danse Macabre). These fantastic illustrations became very popular in early medieval times. They were meant to emphasize the uncertainty of life and the essential equality of all men. The points emphasized were that death came to all men unbidden and often unexpected, and that death made all equal. The usual arrangement of such a series showed death, depicted as a skeleton, coming to take various individuals, from the most eminent to the most lowly. All groups, the pope, cardinals, kings, nobility, clergy, religious, professional men, beggars, fools, thieves, etc. were all shown in their typical clothing and occupation. Almost invariably the doctor was depicted in his long robe and in the act of examining a glass of urine.

The earliest of these representations were quite crude, but some of the later ones became true works of art. The most famous is the series of Hans Holbein the younger, the Dutch artist and painter who came to England to be the court painter for Henry VIII and whose paintings of the eminent people of Henry's court are treasured today by the finest galleries. His Totentanz series includes, of course, the physician who sits in his study in his long robe. Death, rather than coming to announce his presence to the physician, leads

in an old man whose urine he holds up for the doctor's inspection (fig. 10). Alfred S. Warthin, who in 1931 published an entire book on the physician as depicted in the Dance of Death shows that this scene was copied and recopied with various degrees of alteration through literally dozens of other books and it has become the most famous of its type. More modern designs on the same subject have failed to capture the dramatic force of this scene of Holbein's and it remains unrivaled to this day.

The last of the well known uroscopists in western Europe was one Michel Schuppach (1707–1781) who lived in Langenau, Switzerland. He had a large following and people came to him from many parts of Europe. He made his diagnosis after a brief questioning and inspection of the urine and then gave out his own medications.

Since that time, uroscopy as such has declined in popularity, and it is almost unheard of today as a sole method of diagnosis. In a few rural areas, amateur uroscopists apparently still operate, some (such as seventh sons) supposed to have special or supernatural powers similar to those who practice hydromancy by which water is located for wells, etc.

Today only the urologist continues to look at the urine. In all other branches of medicine the physician is content to read a report of the laboratory examination. However, examination of the urine remains a necessary part of every complete medical examination and in this sense, the ancients were not wholly in error in their estimate of its importance.

Present day gross examination of the urine in the form of the two glass test may reveal important information as to the site of disease in the lower urinary tract. It is surprising that the uroscopists, despite their minute division and subdivision of signs, never divided the specimen into a first and second portion. The clinical laboratory has grown to such an extent that the urine examination while essential, is only a tiny fraction of its whole work. But there are those who fear that the laboratory is once more overshadowing the history and physical examination in the diagnostic scheme. They assert that too often these are becoming perfunctionary preludes to the reading of a sheaf of reports in triplicate.

And thus we see that the ancient method of examining the urine, uroscopy, was the only equivalent of our present clinical laboratory tests for many hundreds of years. It passed through phases when it was the most important, or even the only method of diagnosis. For centuries it was the badge of the medical profession and was the subject of thousands of artistic works, of miniatures, paintings, sculptures, woodcuts, and other artistic efforts. It declined in importance till it was the method of charlatans, quacks, and uromancers and became an object of ridicule and contempt. Today, though still used in a limited way by the urologist, its name is scarcely known to a majority of the medical profession.

25 E. Washington St., Chicago 2, Ill.

REPORT OF A SIXTEEN-YEAR CURE OF A WILMS' TUMOR IN A WOMAN

GEORGE R. LIVERMORE

This case was first reported before this society by me in June 1952.[1] At that time, the patient represented a 10-year survival.

A white woman was first seen by me on June 16, 1941, at the age of 37. Her first urologic symptom was an attack of right renal colic in December 1940. Her local physician made a diagnosis of floating kidney with a kinked ureter, and on December 15, an exploratary operation by him disclosed a perinephric abscess and a renal tumor. A biopsy taken at that time was reported as Wilms' tumor.

The pertinent findings were confined to the right flank and the urinary tract. A draining sinus was still present six months after operation, and mucopurulent material exuded from this. There was a fixed, non-tender mass underlying the sinus and extending down below the crest of the ilium.

Routine laboratory examination was within normal limits. An x-ray of the kidneys, ureters and bladder showed the mass in the lower pole of the right kidney, extending one inch below the iliac crest. Cystoscopy and retrograde pyelography were performed. There was no flow of urine from the right kidney and no excretion of indigo carmine. Pyelograms showed the pelvis on that side to be distorted and pushed up by a large tumor in the lower pole of the kidney.

[1] Livermore, G. R.: Wilms' tumor in an adult: Report of a ten-year cure. J. Urol., **70:** 141-145, 1953.

Because of the size of the tumor and the time factor, a preliminary course of roentgen therapy was prescribed. From June 17 to July 2, she recieved the total of 4,100 r through two portals, delivered by a 200 KV machine. Six weeks later, the mass had decreased in size by about 25 per cent, and was then movable.

The patient was hospitalized, and on August 17, 1941, the tumor was approached through a lumbar incision. The upper two-thirds of the kidney was normal. A huge tumor mass, still the size of a grapefruit (the x-ray therapy had changed our grapefruit from a California to a Florida one) occupied the lower pole. There were many adhesions and the tumor was intimately attached to the vena cava from which it was separated with great difficulty. Our pathologist made a diagnosis of Wilms' tumor, and this has since been confirmed by the Tumor Registry of the American Urological Association.

The patient was last seen on April 15, 1942, at which time she felt entirely well. The wound was completely healed, and she had gained 15 pounds. On February 3, 1958, I received a letter from her stating that she is alive, well, and working daily as a mail clerk. On August 17, 1958 she will have survived 17 years since nephrectomy and almost eighteen years since the first biopsy proved the nature of her lesion.

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DISCUSSION

DR. JOHN LATTIMER (New York, N. Y.): Apropos of the subject of Wilms' tumor, we have gone through our Wilms' tumors at the Columbia-Presbyterian Medical Center, recently and have found 71 cases.* We have broken them down into two groups: those before 1932 and those since 1932. The treatment of the group before 1932 was disappointing. We have had much more effective radiotherapy since 1932, and we have more or less standardized our program of treatment, namely, prompt operation and then vigorous postoperative radiotherapy.

The comparison of the results of treatment in the two groups is similar to the Boston reports of the past, namely, that post-treatment survival has been greatly increased. The total survival in the pre-1932 group ran around 10 per cent, and since 1932 the total survival has been around 40 per cent. Of those operated on in the latter group the survival is even better; i.e., 44 per cent.

[Slide] The cases that have been treated since 1932 are 42 in number. The patients have all been followed for at least two years. There were 36 cases operated on in this series, with a 53 per cent two-year survival for the entire group. As I will show later, the two-year survivals appear to be pretty significant.

[Slide] These are the different treatment regimens which were used. Five patients were not treated because they were in very bad condition and inoperable.

Radiotherapy by itself did not work well. In the preoperative radiotherapy group only one patient survived out of the five, for two years. The largest group was treated by immediate nephrectomy and postoperative radiotherapy, with a 47 per cent survival.

Strangely enough, four out of the five who had nephrectomy alone are alive, emphasizing that these tumors do vary tremendously in malignancy. There are other unknown factors which enter into the prognosis and we have no way of predicting the outcome. We have no way of predicting duration of survival, in advance. The entire group of 42 patients has been followed for at least two years. The longest survival is something over twenty years.

* J. Urol., **80:** 401–416, 1958.

[Slide] This slide shows the year of death. There were no operative deaths. Eighty-five per cent of those who died, died within two years. The only child who died after a longer interval than four years, died of hydronephrosis, and had a stricture of the ureteropelvic junction. The mother refused to bring this patient back for followup. The hydronephrosis increased, and the child died 10 years later, of uremia.

[Slide] This slide indicates the factors that had to do with survival. Those with encapsulated tumors did best. Those with renal vein invasion did not do well, although some of them did all right, as was pointed out the other day by Dr. Gershom J. Thompson. Those with a torn capsule or frank invasion through the capsule at the time of operation did very poorly.

[Slide] The location and extent of the tumor, as you might expect, had a good deal to do with prognosis. If the entire kidney was involved, the results were very poor. If it was an upper pole tumor there was a 29 per cent survival, whereas the lower pole tumors did very well. As you might expect, the lower pole tumors could be palpated more quickly and could be approached more easily.

[Slide] As to symptoms and signs, all had a mass. The sedimentation rate was a very valuable prognostic point. Those with a very high sedimentation rate all died. The blood pressure was up in 60 per cent, which was surprising. This has been reported before, incidentally. Gross hematuria was 12 per cent, which was a little greater from what we had expected before the figures were reviewed.

[Slide] Factors with unfavorable prognosis: Children diagnosed after two years of age had a poor prognosis, as I will show you in a moment. Those who had a penetrated capsule, those with vascular invasion, those with metastases, those with a high sedimentation rate and anemia, and those with upper pole tumors, all had a bad prognosis.

[Slide] The year diagnosed in this group: A great many of them were diagnosed in the first year, and not so many after the fourth year.

[Slide] This shows survivals. Those who were treated under age 2—in other words, when we picked them up and operated on them or treated

them before age 2—did wonderfully well, with a 73 per cent survival. Those under 6 months of age had an 80 per cent survival. Those treated over 3 years of age had only an 18 per cent survival. This was not just a matter of discovering them late, because the weight of the tumor was relatively constant throughout the series; prognosis has more to do with the nature of the tumor than when you discover it.

Incidentally, one of these patients was operated on at four days of age, which is very early. One of them was picked up as a very tiny tumor by one of our medical students who was doing an examination for cryptorchism.

[Slide] Finally, just as a matter of interest, we went through a lot of our cases of children with abdominal masses, to see what the masses were. First we excluded all the obvious large spleens from Banti's syndrome, and so on. The remaining masses were divided about half and half between the renal and the nonrenal. There were 139 renals and 146 nonrenals. The renals were about evenly split. These, incidentally, are children in whom masses could be palpated, and usually the chief complaint. The renal masses were approximately evenly divided among Wilms' tumor, hydronephrosis and cystic renal lesions. About half were intraperitoneal and half were extraperitoneal.

This is a matter of some importance to us in fending off those who call themselves pediatric surgeons, who are moving in on the Wilms' tumor field in many parts of the country and trying to set up pediatric surgical residencies.

To have these data in order to be able to state that half of the abdominal masses will be renal, and a very large proportion will be benign, hydronephrotic, and so on, is of some interest to us as a group in the campaign that is going to face us in the coming years in maintaining urology and keeping it for the urologists.

Incidentally, apropos of this, we have found that in the cases of Wilms' tumor, in which a retrograde pyelogram had been done, the diagnosis was accurately made in every case. On the other hand, if only an intravenous pyelogram had been made, you could not always tell what it was in advance.

The philosophic or even the practical question comes up as to whether a retrograde, with a second anesthetic perhaps, is indicated in these tiny babies with a mass which might turn out to be malignant, and whether it is justifiable or is not.

Let me say again that from observation of these cases, those who did have a retrograde had an accurate diagnosis made in every case.

DR. NESBIT: I want to report further on the patient whose case I reported, I believe at our 1950 meeting. This man had a pulmonary lesion discovered when he was having his Draft Board examination in Detroit. The microfilm disclosed a lesion in the lower lobe of his lung. When this was found, the physician who examined him asked him what his medical history was. He said he had had a Wilms' tumor removed by me 17 years previously. He had been reported as one of our cures.

The young man was urged to return to me, so he went to Ann Arbor and we made stereoscopic x-rays of his chest. Sure enough, he had a lesion about the size of a tennis ball in the lower lobe of his right lung.

Interestingly enough, he had been in our clinic only one year earlier for reasons I have never learned, and we made a chest film on him exactly one year prior to the last one when the diagnosis was made. That x-ray was negative.

This young man was 17 years postoperatively at the time the pulmonary lesion was found. Dr. Cameron Haight removed it by lobectomy. It was identical in structure to the primary tumor that had been removed seventeen years before.

I received a Christmas card from him last Christmas which coincidentally was the birth announcement of his first child, and in gratitude they named the child for me. (Laughter)

So, a seventeen-year survival does not mean a seventeen-year cure even for a Wilms' tumor.

VOICE: How long since his pulmonary resection?

DR. NESBIT: Eight years.

DR. WILLARD GOODWIN (Los Angeles, Cal.): I would like to mention briefly an unusual series of events in a child who had bilateral Wilms' tumors.

About two and a half years ago a four-year-old boy had removal of the right kidney by my former associate, Dr. David Gray, and a typical Wilms' tumor was found. The child was treated with x-ray. About six months later (two years ago now) he had a recurrence or a new tumor, I don't know which, in the opposite kidney, an obviously palpable mass, huge in size. It was felt to be inoperable and incurable. The family insisted that something be done about it.

The child was uremic because the mass was obstructing the ureter, so we explored the patient

in the vain hope that something might be done surgically. It was impossible. We took a piece of wire and outlined the periphery of the tumor, which left a thin rim of kidney at the top. Then the radiologists were willing to treat it with x-ray. Now, two years later, the mass has vanished. The child is active and is living a healthy life. I think it is too much to believe that he is cured, but it is quite important that he has had two good years of life, and the family has had two years of his company.

No biopsy was taken at the time of the second operation because we thought it would be meddlesome. There was no question, however, about its being a neoplasm.

DR. REED M. NESBIT (Ann Arbor, Mich.): Dr. Goodwin, I would like to comment on the case you have just discussed because in our series there was a case diagnosed by pathologic material obtained by a punch biopsy, which horrified me. The child is a moron and has survived now over twenty years following irradiation of that Wilms' tumor which was palpable and treated, incidentally, by only a minimal amount of irradiation. The child is still living. We have a report on him annually because he is in one of our foundling homes in the State of Michigan.

PRESIDENT CAHILL: We all know about the spontanous regression of tumor by itself. Anything can happen, but at least the latter part of this discussion has been very fruitful and very interesting.

Are there any further discussers?

DR. MEREDITH CAMPBELL (Miami, Fla.): Just for the record, in connection with Dr. Livermore's presentation, I saw in consultation a 29-year-old woman who had a scalp metastasis 24 years after removal of a Wilms' tumor, verified histologically.

PRESIDENT CAHILL: There is one important person to bring forward at the end of this meeting. I will ask Dr. Charles A. W. Uhle and Dr. Vincent J. O'Conor, Sr. to escort Dr. John A. Taylor, our new President, to the Chair so that we may induct him into office with all the propriety that goes with this exalted office.

PRESIDENT CAHILL (continuing): Dr. John, I herewith give you the gavel of your office. May you enjoy the position as much as I have, sir.

PRESIDENT TAYLOR: Gentlemen, I consider it a great honor to be President of this grand society. I am proud of it, but at the same time I am humble when I think of the men I am succeeding. I shall do my best to carry the torch.

If this meeting is an example of what Dr. William J. Engel, Secretary, can do with your cooperation, I am sure you are going to have a good meeting at Seaview. I have been a member of Seaview for years, and I shall do my best to see that you are comfortable. We have new meeting rooms, and we don't need a five-minute hiatus to connect the microphone. We have nine new golf holes which are the finest in the country, giving golfers thirty-six holes in which to lose themselves.

So, leaving the past with Hippocrates, Galen and Josephus Kieferus, let us march forward under the shibboleth of "On to Absecon!" (Laughter and Applause.)